Risk factors and costs of developing surgical site infection after primary hip arthroplasty in Norway

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Preface

This document is a master thesis for the degree of Master of Philosophy (M. Phil.) in Health economics, policy and management at the University of Oslo. It was developed during my internship at the Norwegian Institute of Public Health (NIPH). Register data from the Norwegian Surveillance System for Antibiotic Consumption and Healthcare-Associated Infections (NOIS) were provided by NIPH while clinical experts provided data on clinical management of surgical site infection. Unfortunately, we received response from only one of the experts that were invited to provide data despite of two reminders. The work was undertaken with keen support from employees at NIPH that offered a working area and access to computer facilities for the data files.

I am very grateful for the opportunity offered by NIPH and I would like to thank my supervisor Professor Ivar Sønbø Kristiansen for his guidance and support throughout the writing of the thesis and supervisor Hanna Merete Eriksen for always giving enlightening advice and positive feedbacks.

Abstract

Background A patient who developed a surgical site infection (SSI) after hip arthroplasty was likely to having an extended length of stay in hospital and incurring additional costs in terms of bed-days, diagnostic and therapeutic interventions, etc. It would be important to identify any patient-, surgical- and hospital-related factors that could be modified before surgery to control and decrease the risk of post-operative infection.

Aim Identify the risk factors for SSI after primary hip arthroplasty, as well as to estimate the hospital cost of SSI in Norway.

Method Risk factor analysis was a register based retrospective cohort study at the national level in Norway including patients undergoing hip arthroplasty between September 2012 and December 2014. Binary logistic regression models were constructed for assessing relationships between the outcome variable (SSI) and a series of explanatory variables. For cost analysis**,** a bottom-up approach was adopted. Health care resources utilized for SSI treatment and the quantities of these resources were derived from an expert survey. Unit costs for the resources were obtained from various sources, including Diagnosis Related Groups (DRG) price list, the Norwegian Medicines Agency database, etc. Total cost of SSI was then calculated by multiplying the quantities of resource use (q) by the unit costs (p) of the resources.

Result During the study period, 17,762 total hip arthroplasty operations and 7,334 hemiarthroplasty procedures were registered in the NOIS. The incidence of SSI after THA was 2.2% (390 of 17,762) and that after HA was 3.6% (264 of 7,334). According to the multivariate regression model, the risk factors for SSI after THA were age, male sex, ASA score $\geq$ III, surgery lasting more than 120 minutes, elective surgery, cement-less fixation and post-operative hospital stay. Perioperative antibiotic prophylaxis and specialty hospital were associated with lower risk of SSI. For HA, the risk factors were fewer, including male sex, cement-less fixation and post-operative hospital stay.

The average cost of a SSI after primary hip arthroplasty for hospital was NOK 198,121. The main cost drivers were readmission stay (56%), followed by reoperation (28%) and additional LOS (11%).

Conclusion Of all the risk factors detected in this study, cemented prosthesis and perioperative antibiotic prophylaxis are the modifiable ones and therefore recommended to orthopedic surgeon and infection control personnel for controlling and reducing SSIs following THA. Given these two are common practice in Norway, further studies could focus on including more explanatory variables in risk analysis or on analyzing the effect of various parameters of perioperative antibiotic prophylaxis and cement fixation (such as the time, route and dosage of administration) to establish more effective preventive interventions.

Surgical site infection following primary hip arthroplasty causes significant economic burden for Norwegian hospitals, mainly due to substantial increase in hospital stay and the resource demanding nature of its revision procedures. The high cost of SSI implies that substantial cost savings can be achieved by reducing the number of SSIs, and in turn, highlights the importance of detecting modifiable risk factors for SSI.

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List of abbreviations

SSI	Surgical Site Infection
DAIR	Debridement, Antibiotics and Implant Retention
THA	Total Hip Arthroplasty
HA	Hemiarthroplasty
NHFR	Norwegian Hip Fracture Register
NAR	Norwegian Arthroplasty Register
HCAI	Healthcare-associated Infection
NARA	Nordic Arthroplasty Register Association
CDC	Centers of Disease Control and Prevention
NINS	Nosocomial Infection National Surveillance
LOS	Length of Stay
ASA	American Society of Anesthesiologists
AR-DRG	Australian Refined Diagnosis Related Groups
NOIS	Norwegian Surveillance System for Antibiotic Consumption and Healthcare-Associated Infections
DRG	Diagnosis Related Groups
NNIS	National Nosocomial Infections Surveillance
NOMA	Norwegian Medicines Agency
NIPH	Norwegian Institute of Public Health
RHA	Regional Health Authority
NOK	Norwegian Krone
NIS	National Inpatient Sample
GBP	British Pound
AUD	Australian Dollar
USD	United States Dollar

1 Introduction

Surgical site infection following primary hip arthroplasty is one of the severe complications that could lead to increased morbidity, mortality and high cost (C. Edwards, A. Counsell, C. Boulton, & Moran, 2008; Coello et al., 2005). It is very important that surgeons as well as infection control personnel are able to identify potential risk factors for developing SSI and implement preventive measures accordingly.

Coello and co-workers (Coello et al., 2005) investigated the adverse impact of SSI for nine defined categories of surgery, including limb amputation, small/large bowel surgery, vascular surgery, coronary artery bypass graft, hip prosthesis, knee prosthesis, open reduction of long bone fracture and abdominal hysterectomy, in English hospitals and found the impacts differed greatly across categories. This highlighted the importance of measuring the impact for individual category rather than for all SSIs and all surgical procedures.

Whilst some studies about the impact of surgical site infection following primary hip arthroplasty have been conducted, little work exists providing an economic perspective. This thesis contributes to knowledge by analyzing risk factors for and resource consequences of SSI, in order to identify target areas for infection prevention and by that the cost of SSI. These results can also be used to inform subsequent cost-effectiveness analyses that evaluate the efficiency of interventions to reduce the risk of SSIs.

2 Background

As showed in **Figure 1**, a hip joint is a “ball-and-socket” joint where the ball is the femoral head and the socket is a "cup-shaped" component of the pelvis called the acetabulum, uniting two separate bones: the femur (also known as thighbone) and the pelvis. As in all the other joints, between the acetabular cup and the femoral head there exists a cartilage to lubricate their movement and facilitate the articulation (Rabiei, 2009). The primary purposes of hip joints are to support the weight of upper body during standing, walking or running, and help with body movements like stretching and bending.

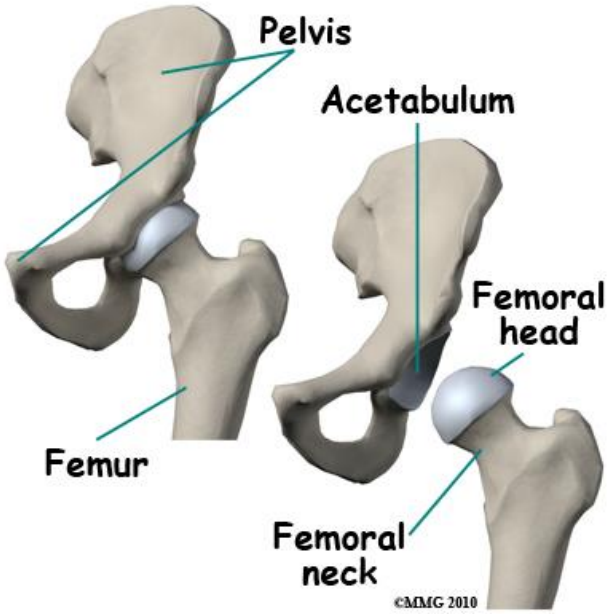

Figure 1 Illustration of the anatomy of hip joint (Source: Medical Multimedia, www. medicalmultimediagroup.com)

When the natural hip joints are impaired and cause persistent pain or problems with daily activity due to reasons like osteoarthritis (cartilage inside hip joints becomes worn away), hip fracture, rheumatoid arthritis (body immune system attacks the lining of hip joints), etc., it might be necessary for the patients to have a hip arthroplasty.

Hip arthroplasty (used synonymously for hip replacement in this study) is an orthopedic surgery where the damaged parts of hip joint being removed and replaced by artificial ones (known as prosthesis) to relieve pain and restore mobility. This reconstructive procedure, which can be either total hip arthroplasty (THA) or a hemiarthroplasty (HA), has improved the management of those hip joint diseases that have responded poorly to conventional medical therapy (Rabiei, 2009).

As a surgery that usually carried out in older adults, the number of hip arthroplasty done will increase as population is aging. Kurtz and colleagues (Kurtz, Ong, Lau, Mowat, & Halpern, 2007) reported a projected increase in THA numbers of 174% to 600,000 procedures per year in the United States from 2005 to 2030. In Norway, each year there are more than 10,000 people having their hip joints replaced, entirely or partly (N. A. Register, 2015). The problem of osteoporosis and other hip joint diseases that require hip arthroplasty is likely to be a growing

burden to society in the near future as life expectancy in Norway is still increasing and the absolute number of older persons at risk of damaging hip joint is expected to increase.

2.1 Total hip arthroplasty (THA)

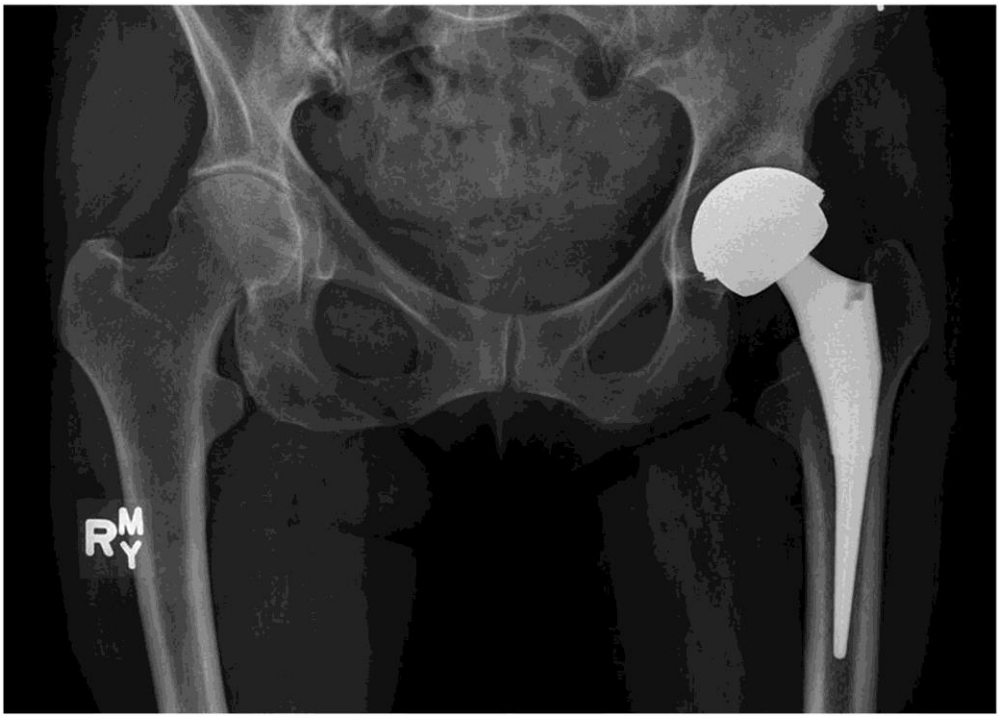

Figure 2 Anteroposterior pelvic radiograph for a patient who had metal-on-metal total hip arthroplasty (Williams, Greidanus, Masri, Duncan, & Garbuz, 2011)

A total hip arthroplasty involves the femoral component fitting into the top of the femur to replace the ball of the ball-and-socket joint, and the acetabular cup sitting in the pelvis to replace the socket. Since its introduction in the 1960s, total hip arthroplasty has become one of the most successful and frequently undertaken elective surgeries with a dramatically improvement in function restoring and a great degree of patient satisfaction (Ackerman, Graves, Bennell, & Osborne, 2006). After reviewing twenty-six studies on total hip arthroplasty, Ethgen and coworkers (Ethgen, Bruyère, Richy, Dardennes, & Reginster, 2004) concluded that total hip arthroplasty was effective in terms of improvement in health-related quality-of-life dimensions, with the occasional exception of the social dimension.

The demand for THAs has been increasing in the last two decades. According to the Norwegian Arthroplasty Register (N. A. Register, 2015), the number of primary THAs performed in Norway has increased from 4606 in 1994 to 8099 in 2014.

2.2 Hemiarthroplasty

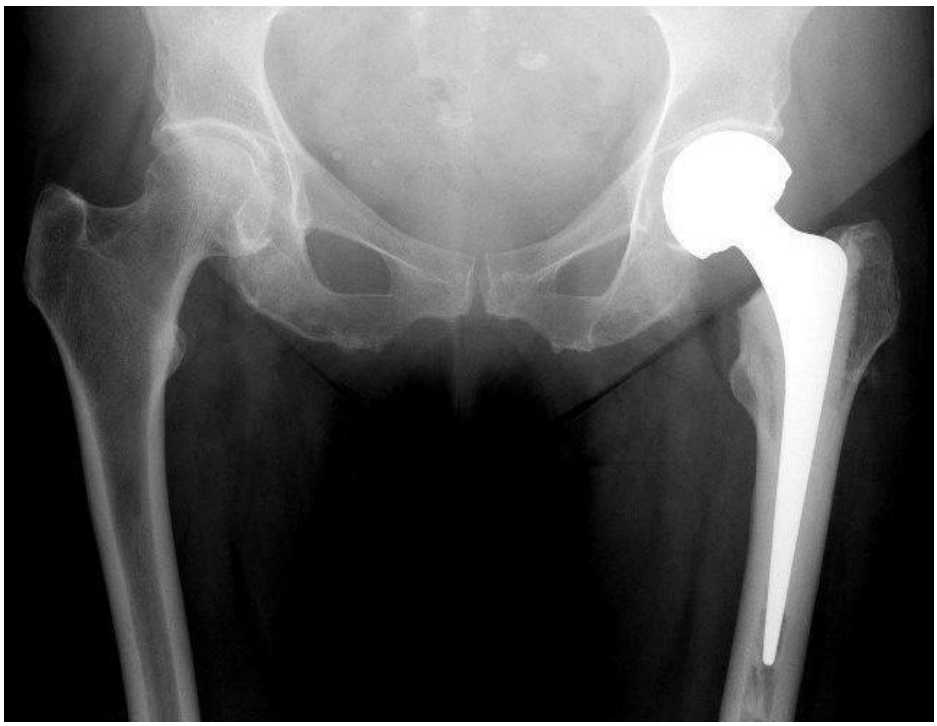

Figure 3 X-ray of a patient who had a unipolar hemiarthroplasty (Cash, Bayer, Logan, & Wimhurst, 2010).

This anteroposterior radiograph shows the femoral component (Exeter Trauma Stem) and the normal, native acetabulum.

Different from THR, a HA involves only the prosthesis replacement of femoral part of the hip joint. The most common reason for HA is hip fracture. In Norway, HA due to hip fractures should be reported to the Norwegian Hip Fracture Register (NHFR). In 2014, the number of hip fractures reported in NHFR decreased slightly from 9284 to 8956 (N. A. Register, 2015). Meanwhile more and more dislocated fractures were treated with hemiarthroplasty since 2005 (**Figure 4**).

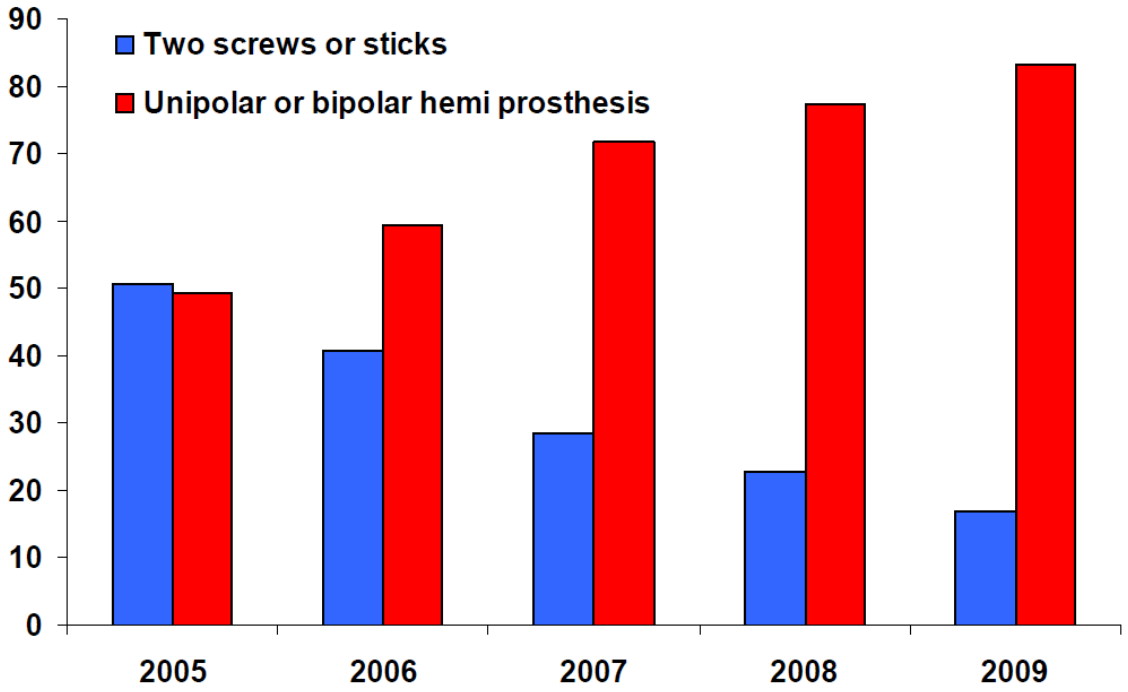

Figure 4 Percentage of displaced intracapsular fractures treated with two screws or sticks, or a unipolar or bipolar hemi prosthesis according to the Norwegian Hip Fracture Register (T. N. A. Register, 2010)

2.3 Revision after primary hip arthroplasty

Revision after primary hip arthroplasty is defined as a surgical procedure that involves exchange or removal of prosthesis. According to the Norwegian Arthroplasty Register (N. A. Register, 2015), for patients had revision procedures in 2014, the most common cause for revision surgery was acetabular loosening (24%), followed by femoral loosening (16%), deep infection (15%) and dislocation (12%). Deep infection has since 2010 exceeded dislocation to be the third most common reason for revision.

2.4 Surgical site infection after primary hip prosthesis

Hip replacement surgery, like other surgical procedures, carries a risk of complications. The most common complications after primary hip prosthesis are instability, aseptic loosening, periprosthetic fracture, infection, and occasionally death. While total hip arthroplasty has progressed to become one of the most successful surgical procedures, infection remains a serious and common complication (Senthi, Munro, & Pitto, 2011). In a recent point-prevalence survey of inpatients conducted in the US (Magill et al., 2014), surgical site infection, which accounted for 21.8% of reported infection, was identified as the most frequently occurring healthcare-associated infection (HCAI) along with pneumonia infection. A study (Dale et al.,

2012) based on the Nordic Arthroplasty Register Association (NARA) dataset from 1995 to 2009 reported that 0.6% of the primary THAs were revised due to infection during that period. In addition, compared with the period 1995-1999, the relative risks of revision due to infection in 2000-2004 and 2005-2009 increased from 1.1 to 1.6 in four countries (Denmark, Finland, Norway and Sweden) and this risk increasing confirmed the earlier findings from Norway (Dale, Hallan, Espehaug, Havelin, & Engesæter, 2009).

2.4.1 Surgical site infection

Infection could be defined as "invasion and multiplication of microorganisms in body tissues, causing cellular injury and inflammatory response" (Dale, 2013). Though different publications use different criteria for surgical site infection, the most commonly used ones are the Centers of Disease Control and Prevention (CDC)'s criteria for postoperative SSI. The CDC criteria divides SSIs into incisional SSIs, which are further classified as superficial incision SSIs, deep incision SSIs, and organ/space SSIs for surveillance classification purpose (Teresa C. Horan et al., 1992). The CDC definitions (**Table 1**) of SSIs have been applied consistently by surveillance and surgical personnel in many settings and currently are a *de facto* international standard (Løwer, Eriksen, Aavitsland, & Skjeldestad, 2013; Teresa C. Horan et al., 1992).

Table 1 CDC definitions of SSIs (Teresa C. Horan et al., 1992)

Superficial infection	Occurs within 30 days of surgery, involves only skin and subcutaneous tissue and meets at least one of the following criteria: 1. Purulent drainage from superficial incision 2. Organisms are grown and pus cells seen from aseptically obtained swab/tissue from the superficial incision 3. At least one of the following symptoms or signs: pain or tenderness, localized swelling, redness or heat, and a) the clinician diagnoses an infection or b) the superficial incision is deliberately opened by a surgeon to manage the infection, unless the incision is culture-negative.
Deep infection	Occurs within 30 days (no implant) or one year (implant) of surgery, involves deep fascia and muscle layers and appears to be related to the procedure and meets at least one of the following criteria: 1. Purulent drainage from the deep tissue but not the joint or bone 2. Organisms are grown and pus cells seen from aseptically obtained swab/tissue from the deep incision 3. A deep incision which spontaneously dehisces or is opened by the surgeon when the patient has fever (> 38˚C), localized pain or tenderness, unless the incision is culture-negative 4. An abscess or other evidence of deep infection found during re-operation, or by histopathological or radiological examination
Organ/Space infection	Occurs within 30 days (no implant) or one year (implant) after surgery. Involves joint and/or bone related to the site of the operation with any other tissues.

	Appears to be related to the procedure and meets at least one of the following criteria: 1. Purulent drainage from a drain which is placed through a stab incision into the joint 2. Organisms are grown and pus cells seen from aseptically obtained swab/tissue from the joint/bone 3. An abscess or other evidence of joint/bone infection found during re-operation, or by histopathological or radiological examination 4. The patient has at least two of the following signs or symptoms with no other recognized cause: joint pain, swelling, tenderness, heat, evidence of effusion or limitation of movement and at least one of the following: a) Organisms and white blood cells seen on Gram stain of the joint b) Positive antigen test on blood, urine, or joint fluid c) Cellular profile and chemistry of joint fluid compatible with infection and not explained by an underlying rheumatological disorder d) Radiological evidence of infection, e.g. abnormal findings on radiographs, CT scans, MRI, radiolabeled scan (gallium, technetium, etc.)

SSIs have been reported to occur in 0.5% - 2.5% of primary total hip arthroplasty, and estimates vary across countries due to different surveillance or register methods, study periods, patient demographics and of course difference in the risk of SSI (Merollini, Crawford, & Graves, 2013; Namba, Inacio, & Paxton, 2012 October; S. Ridgeway et al., 2005; Vicente Monge Jodra , Lourdes Sainz de los Terreros Soler , Cristina Díaz - Agero Pérez , Carmen María Saa Requejo , & Nieves Plana Farrás 2006).

Not only resulting in increased morbidity, mortality (Awad, August 2012) and reduced functional outcomes in patients, SSIs also impose a considerable economic burden to patients and their families by prolonging the duration of hospital stay, causing additional surgery and increasing costs (Broex, van Asselt, Bruggeman, & van Tiel, 2009; Chen, Chou, & Chou, 2005; Coello et al., 2005).

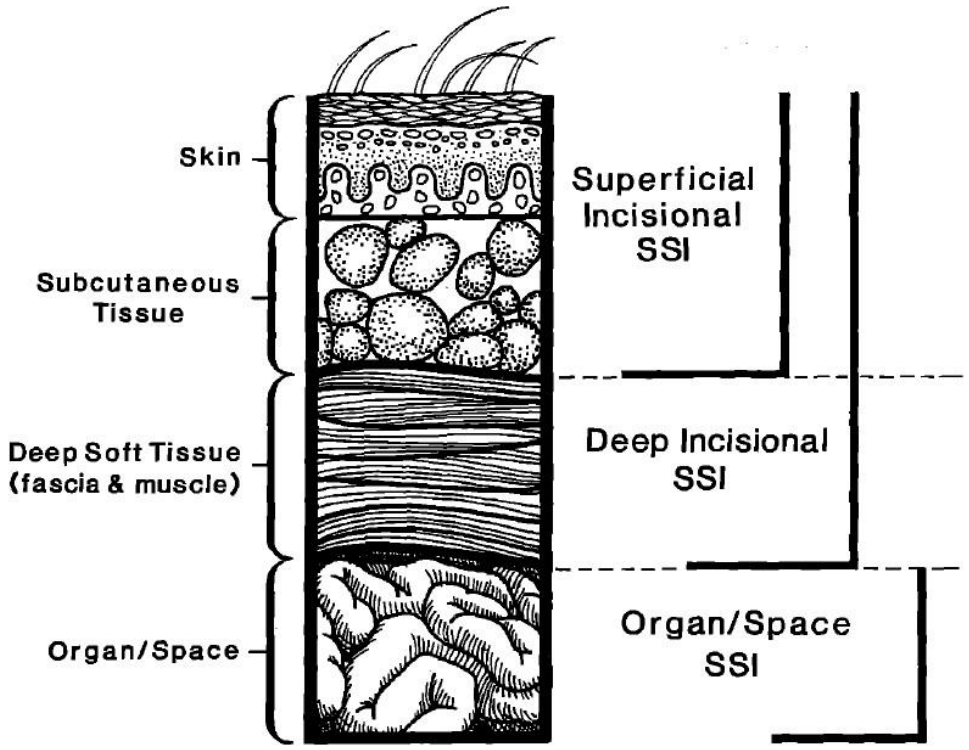

Figure 5 Cross-section of abdominal wall depicting CDC classifications of surgical site infection (Teresa C. Horan et al., 1992)

2.4.2 Risk factors for SSI after THR/HA identified in literature

Whether a wound becomes infected after surgery depends on a complex interaction between patient-related, surgical-related, and microbial-related factors. Optimal application of SSI prevention measures often requires targeting a variety of risk factors. In the context of SSI, the term risk factor refers to a variable that has a significant, independent association with the development of the infection (Alicia J. Mangram et al., 1999).

A variety of risk factors for infection after THA and HA have been reported. A British study (S. Ridgeway et al., 2005) based on the Nosocomial Infection National Surveillance (NINS) service data found that age, female gender, American Society of Anesthesiologists (ASA) score, body mass index (BMI), trauma, duration of operation and pre-operative stay were significantly associated with the risk of SSI after THR while for HA, only ASA score and age were significant factors. The multivariate analysis identified age ≥ 80, trauma, duration of operation > 120 minutes and ASA score ≥ III as significant independent risk factors for SSI, regardless of the type of hip arthroplasty. These findings are in line with the reported results from a similar study (Namba et al., 2012 October) done in the US. In 2011, Dale and colleagues (Dale et al., 2011) assessed the risk factors for infection after hip arthroplasty using data from the Norwegian Arthroplasty Register (NAR), the Norwegian Hip Fracture Register (NHFR) and

the Norwegian Surveillance System for Antibiotic Consumption and Healthcare-Associated Infections (NOIS), and found advanced age, ASA class higher than II and short duration of surgery were risk factors for SSI after THA.

2.4.3 Management of SSI

Superficial SSIs usually do not have a big impact on patients' quality of life and are typically treated with simple measures like superficial debridement, local drainage and oral antibiotics. Deep or organ/space infection, on the other hand, involves the muscle, fascial planes or organ, can have devastating consequences for the patients and typically require revision surgery, including one-stage exchange revision and two-stage exchange revision, or in the most severe cases permanent removal of the prosthesis (Resection procedure) (Urban, 2006). One-stage exchange is one surgery that involves both the extraction of prosthesis and implantation of a new prosthesis. While in two-stage exchange revision, the extraction and implantation are conducted separately in two surgeries where the new prosthesis is implanted in the second surgery 2 to 12 weeks after the first one. In the absence of a universally accepted protocol, the management of deep or organ/space SSIs is multidisciplinary and challenging; patients are generally managed on a case-by-case basis taking account of individual factors. A recent retrospective analysis conducted in Australia (Merollini et al., 2013) showed that the majority (74%) of patients experienced early infection onset were first treated with debridement, antibiotics and implant retention (DAIR). The following first treatments were one-stage revision and two-stage revision with 89.7% and 92.9% success rate respectively. A Swiss study (Betsch, Eggli, Siebenrock, Täuber, & Mühlemann, 2008), however, reported the most common treatment strategy to be two-stage revision (75%), followed by DAIR (17.6%) and one-stage revision (5.9%). Aside from Switzerland, 2-stage revision, the old golden standard in treating deep or organ/space SSIs, is also the preferred treatment in the US (Lentino, 2003).

In Norway, about 50% of the revision surgeries reported in the National Arthroplasty Register (NAR) were debridement and retention of the infected implant, 25% were two-stage exchange, 12% of one-stage exchange and the remaining 13% were resection arthroplasty (Girdlestone procedure). For patients who had poor health status or short life expectancy, long-term antimicrobial suppression was an alternative treatment to revision surgery. This procedure is not reported to NAR, so to what extent the long-term suppression is used in Norway remains unknown.

2.4.4 Economic burden of SSI

A number of studies have been conducted to estimate the economic burden of SSI (Broex et al., 2009; Jenks, Laurent, McQuarry, & Watkins, 2014; Urban, 2006). These researches revealed that patients with SSI often require longer time in hospital, more nursing care, additional diagnostic tests and, sometimes, revision surgery and readmission to hospital, thereby posing heavy economic burden to health care sector. The magnitude of the economic impact, however, varies widely across studies, mainly due to the inconsistency of study methods, cost components included, perspective adopted and hospital reimbursement systems.

Katharina M.D. Merollini and colleagues conducted a retrospective analysis (Merollini et al., 2013) in 2013 to estimate reimbursement costs of surgical site infections after hip arthroplasty in Australia. In this study, treatment costs were estimated based on Australian Refined Diagnosis Related Groups (AR-DRG) cost accounting codes assigned to each patient hospital episode. The authors found that patients who were first treated with debridement, antibiotics and implant retention (DAIR) had an average cost of AUD 13,187 (NOK 80,915), while those first treated with one-stage revision and two-stage revision had average costs of AUD 27,006 (NOK 165,708) and 42,772 (NOK 262,447) respectively. Patients had excision arthroplasty on average costed AUD 23,805 (NOK 146,066). Overall, the total average treatment cost per deep SSI was AUD 24,644 (NOK 150,828) across all treatment modalities.

A recent study from UK by P.J. Jenks and coworkers (Jenks et al., 2014) assessed the economic burden of SSI over a two-year period based on SSI surveillance data, patient level information and costing system dataset. The median additional length of stay (LOS) attributable to SSI reported in this study was 10 days (95% confidence interval (CI): 7-13 days); the median additional cost attributable to SSI was GBP 5,239 (NOK 67,113) across all categories, and GBP 3,214 (NOK 41,172) (95% CI: 657-17,040) for hip replacement alone. After calculating the opportunity cost of eliminating all SSIs that occurred in the study period, the researchers found that for seven surgical categories, hip replacement included, the hospital would have been financially worse off by eliminating all SSIs. The authors concluded that the current system of reimbursement provided financial disincentive to SSI reduction.

Another Australian study from 2013 by T.N. Peel and colleagues (Peel et al., 2013), on the other hand, examined the overall hospital cost of the treatment of prosthetic joint infection across 10 hospitals over a 3-year period. Cost calculations in this study included hospitalization costs, surgical costs, hospital-in-the-home costs and antibiotic therapy costs. Their findings

showed that the median cost of treating prosthetic joint infection was AUD 34,800 (NOK 212,986). Aside from the cost estimating, the authors also modeled factors associated with the cost and found that compared to cost of DAIR, surgical treatment with one-stage exchange (100% increase; $p = 0.009$) or resection arthroplasty (48% increase; $p = 0.001$), among other factors, were independently associated with increased treatment costs.

A review of cost analysis of surgical site infections by Joshua A. Urban (Urban, 2006) reported that the principal determinants of the SSI costs were the depth of the infection, geographic localization and the type of surgery performed. The costs increased with the depth of the infection. That was, the costs associated with superficial infections were relatively low, but increased with deep and, especially, organ/space infections.

To date, the estimation of SSI cost in Norway has not been examined in great detail even though SSI has been recognized as a costly complication and the incidence rate in Norway has been increasing in recent years (Dale et al., 2009).

2.5 The Norwegian Surveillance System for Antibiotic Consumption and Healthcare-Associated Infections (NOIS)

The Norwegian Surveillance System for Antibiotic Consumption and Healthcare-Associated Infections (NOIS) was introduced in 2005 following a 2004 government strategy of reducing health care associated infections (Løwer et al., 2013). Due to its mandatory nature (95% participation rate in 2009), all patients who undergo at least one of the five specified surgical procedures (coronary artery bypass graft; cesarean section; primary hip prosthesis; cholecystectomy and colon surgery) at any Norwegian hospitals are supposed to be registered in the NOIS.

At hospital level, data were collected before, during, and 30 days after surgery (**Figure 6**). For surgeries involve implant, the follow-up time is extended to one year. More specifically, basic patient information is collected at admission then surgery-related information collected during surgery, followed by patient's infection status being registered by a physician at discharge. Then 25-30 days after surgery, patients are expected to receive a customized and personalized follow-up letter asking for infectious events. The letter contains questions about certain specific signs of SSI and whether the patient has consulted a doctor about these signs. Aside from the questions, the letter also contains classification guidance for doctors who diagnosed the infection (Berg et al., 2011). Reminders are sent to patients who did not respond to the questionnaire and finally, phone calls made to the remaining non-respondents. All SSIs, other

than superficial ones, that have been detected during hospitalization and after discharge are to be confirmed or diagnosed by a physician according to CDC definitions. Superficial infections could be patient reported and are coded separately in NOIS-SSI.

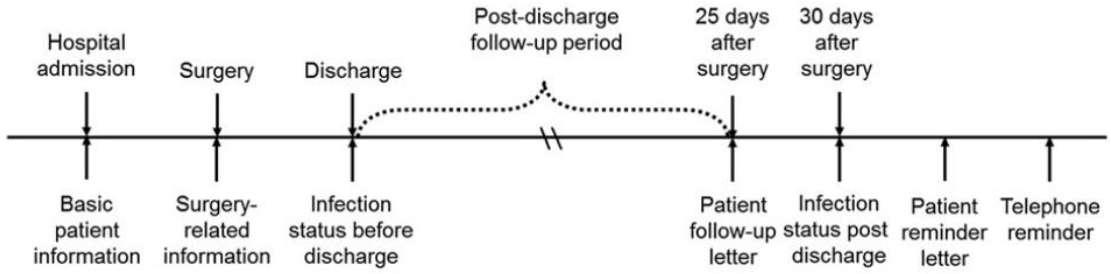

Figure 6 Points in time for collection of information during 30-day follow-up in NOIS-SSI (Løwer et al., 2013)

Up to 2009, 70% (Løwer et al., 2013) of hospitals in Norway have developed or acquired computerized infection control modules (ICMs) in order to harvest data from hospitals' existing systems, initiate patient follow-up letters, establish quality assurance routines and generate statistics or reports for local use and submission of data to national level. Data collected in the NOIS encompasses background and explanatory variables (e.g. patient information, surgery details) and outcome variables (e.g. infection status, readmission). The former ones are almost all being collected by ICMs automatically while the later ones must be entered manually.

After evaluating its first five years of operation H. L. Løwer and colleagues (Løwer et al., 2013) claimed that NOIS has achieved high hospital participation, a reasonable proportion of non-missing variables and 90.7% completeness of 30-day patient follow-up.

2.6 Aims and research questions

The aim of this study is to identify risk factors for surgical site infection (SSI) following primary hip arthroplasty, as well as to estimate the costs of such infection for hospitals in Norway in order to identify target areas to reduce SSI and thereby the cost. The specific research questions were as follows:

- What are the risk factors for SSI following THA and HA respectively?
- What type of health care resources and what quantities are utilized in hospital for treating SSI after primary hip arthroplasty?
- What is the economic burden and main cost drivers for SSI after primary hip arthroplasty for Norwegian hospitals?

following hypotheses were to be tested:

- Age, ASA (the American Society of Anesthesiologists classification system for physical status) score, and prolonged duration of surgery are the most important factors associated with SSI
- SSI following primary hip arthroplasty causes high additional costs for hospitals, mainly driven by prolonged hospitalization, additional diagnostic tests, therapeutic use of antibiotics and revision surgery

3 Data and Methodology

3.1 Data source

Data used in this study came from various sources, including the Norwegian Surveillance System for Antibiotic Consumption and Healthcare-Associated Infections (NOIS), an expert survey, Diagnosis Related Group price list, the Norwegian Medicines Agency, etc.

3.1.1 NOIS data

All primary hip arthroplasty registered in the NOIS during September 2012 to December 2014 were included in this study. The NOIS database contains extensive information on a multitude of subject areas, but important to this study are those listed in **Table 2**.

Table 2 Central variables in the Norwegian Surveillance System for Antibiotic Consumption and Healthcare-Associated Infections (NOIS) dataset

Variable	Definition
Patient	
Age	Age of patients
Sex	Male/Female
ASA score	Score of the six-category physical status classification system that adopted by the American Society of Anesthesiologists
Surgery	
Wound contamination	Clean/Other (clean-contaminated, contaminated and dirty)
Duration of surgery	Surgery time measured in minutes
NNIS risk index	Patients are given a risk point if they have: surgery time over 75 percentile, contaminated or dirty wound or ASA score higher than 2
Perioperative antibiotic prophylaxis	Perioperative prophylaxis used or not
Elective	Elective or emergency surgery
Cement	Cement used or not for prosthesis fixation
Pre-operation stay	Days spent in hospital before surgery
Follow-up time	Time of patient follow-up, ranging from 0 to 30 days
Hospital	
Region	Health region* that a hospital belongs to

Size	The size of a hospital, measured by the number of hospital beds
Type	The type of hospital, categorized based on the level of healthcare the hospital delivered
Cost	
Postoperative stay	Days spent in hospital after surgery
Readmission due to infection	Readmission to hospital due to SSI
Reoperation due to infection	Reoperation due to SSI

* Health region map has been attached as Appendix 1

3.1.2 Expert survey

The survey was designed to elicit clinical management of patients with different types of SSIs after total hip arthroplasty and hemiarthroplasty in Norway. Four orthopedic surgeons working in the four health regions in Norway were chosen as experts from the NOIS reference group. An electronic survey (see Appendix 2-5) was sent to the experts by e-mail during the research period. One of the selected surgeons responded after the first contact while the others did not. Therefore, shortly after the first contact, another two follow-up e-mails were sent out to the non-respondents as reminders, but regrettably, the other three experts had not replied to the survey throughout the whole research period (10 weeks).

In the survey, healthcare resources utilized for the treatment of SSI were listed according to infection severity and experts were asked to identify relevant resource items and to estimate the quantity of each healthcare resource item used based on their empirical experience.

3.1.3 Unit cost

The unit costs of different surgical treatments were based on the reimbursement systems in Norway. With the introduction of activity-based funding in 1997, financing of somatic hospitals in Norway evolved from block grant financing to mixed financing consisting DRG reimbursement (40%) and block grant financing (60%) (Petersen, 2010).

Unit cost for pharmaceuticals were derived from the Norwegian Medicines Agency's price data base (NOMA, in Norwegian: Statens legemiddelverk).

The average cost per day in somatic hospital was based on the Norwegian Directorate of Health's (Helsedirektoratet) 2013 annual report on specialist services in Norway (SAMDATA 2013).

3.2 Study design

Risk factor analysis was a register based retrospective cohort study at the national level in Norway including patients undergoing primary hip arthroplasty between September 2012 and

December 2014. Regression analysis was employed in this study as the statistical tool for assessing relationships between variables. SSI status within 30 days after surgery, defined according to the CDC definition, was used as dependent variable in a logistic regression analysis along with relevant independent variables explaining potential risk factors. These independent variables were subdivided into patient demographics, surgery related characteristics and hospital related characteristics. Likelihood ratio (LR) chi-square test statistic, *p*-value and pseudo R-squared in both bivariate logistic model and multivariate logistic model were used to examine if the model was statistically significant and how well the model fitted.

In terms of the cost analyses, because the mean and median age of total hip arthroplasty and hemiarthroplasty patients were both above 67 years, they could then logically be assumed to have retired from work, thus the costs of absence from work and related productivity losses were excluded in the cost analysis. Besides, data on the costs incurred in the rehabilitation institutions were not available. Therefore, this study mainly takes a hospital perspective.

According to Drummond (Drummond, Stoddart, Torrance, O'Brien, & Stoddart, 2005), there are two elements in costing analysis: measurement of the quantities of resource use and the assignment of unit costs or prices. Therefore, the hospital cost of treating SSI following primary hip arthroplasty was calculated following this equation:

$$Total\ cost\ (TC) = p_a * q_a + p_b * q_b + \cdots + p_n * q_n \qquad (1)$$

Where a, b… n are notions for different kinds of resources

The hospital overhead cost, as well as cost of doctor visits and nursing care were assumed to be part of the cost of hospital days.

In order to quantify the resource used for treating SSI, a clinical "pathway" of SSI treatment after primary hip prosthesis was established based on the review of clinical guidelines and expert opinion. This pathway intends to describe the usual clinical management of SSI. Expert opinion was obtained through a structured questionnaire (see Appendix 2-5) that were sent out to four orthopedic surgeons in the NOIS reference group who respectively represent the four health regions in Norway. Quantification of each resource used was obtained based on the range of quantities of each item given by the expert. Unit costs (**Table 4**) were derived from various sources, mainly from authority document such as the Norwegian Directorate of Health's (Helsedirektoratet) 2013 annual report, Norwegian Medicines Agency, *etc.*

All costs were expressed in terms of 2015 Norwegian Krone (NOK).

3.3 Data Management

Deep infection and organ/space infection are defined as two different infections according to CDC criteria, in this study, however, these two types of infections were combined since physicians have reported difficulty in distinguishing deep infection from organ/space infection or *vice versa* in practice.

Three categorical variables, namely contamination score, ASA score and Nosocomial Infection National Surveillance (NNIS) risk index, were recoded into fewer categories respectively based on evidence from previous literature (Namba et al., 2012 October; S. Ridgeway et al., 2005). Due to the same reason, two continuous variables: duration of surgery and pre-operation hospital stay were recoded into categorical ones.

Missing data:

For the data used in the logistic regression, there were 2150 missing data points across a multiplicity of variables, composing 8.7% of the total data points. In Stata, the default method of dealing with missing data is listwise deletion, also known as complete case analysis, meaning that regression model uses just those cases with complete data for all the variables in the model. This listwise deletion might be a reasonable approach when the discarded cases form a representative and relatively small portion of the entire dataset. However, on the other hand, listwise deletion implicitly assumes the discarded cases represent a random subsample, which may well not be the case in this study since the missing cases could possibly differ systematically from the rest, for example, reoperation data is systematically missing for non-infection cases. Then consequently, estimates made by this method would be biased. Therefore, in order to avoid the possibility of decreasing statistical power, introducing bias and affecting the representativeness of the results, case deletion should not be adopted in risk factor analysis. Instead, a commonly used method of grouping the missing values as another category for each variable was employed to deal with the missing data.

3.4 Analyses

Each analysis performed in this study will be described more thoroughly in this part.

3.4.1 Risk factor analysis

After categorizing indicator variables into three groups, namely patient-related characteristics, surgery-related characteristics and hospital-related characteristics (**Table 2**), descriptive

statistics were computed for all study variables to describe and explore the dataset. The frequency distributions of surgical site infection status among the categories of patient-, surgery- and hospital-related characteristics were compared using chi-square test (or Fisher's exact test when there existed one or more of the cells had an expected frequency of five or less). Continuous variables such as age, post-operative hospital stay and follow-up time were investigated using independent samples *t*-test.

In order to identify and quantify the factors that determined whether or not a primary hip arthroplasty patient developed surgical site infection, a binary logistic regression model was constructed. In this model, infection status was modeled as a function of patient, procedure and hospital characteristics. Outcome variables describing patients' infection status had two categories, 0 and 1, representing no infection detected in one case and infection detected in the other case.

Let y be the observed binary outcome variable indicating no infection and infection with numbers 0 and 1 respectively; x was an individual independent variable. The estimated probability of infection ($y = 1$) given x could then be noted as $\pi(y|x)$. It is the probability of being infected that was modeled in relation to a series of independent variables.

The logistic regression model is:

$$\ln\left[\frac{\pi(y|x)}{1-\pi(y|x)}\right] = \beta_0 + \beta_1 * x_1 + \beta_2 * x_2 + \cdots + \beta_k * x_k$$

Where x_k was the individual explanatory variable, β_k was the estimated coefficient for x_k

Independent (explanatory) variables included in the regression model

Variables deemed to be possible risk factors for SSI from previous literatures were included as independent variables. In addition, exploring the effects of hospital region; hospital type and hospital size on the probability of developing SSI was possible given having relevant data in the NOIS dataset. All the independent variables were grouped into patient characteristics, surgery characteristics and hospital characteristics.

Patient characteristics

Patient characteristics were measured using age, gender and ASA physical status. ASA score is an assessment by the anesthesiologist of the patient's preoperative physical condition using the American Society of Anesthesiologists' (ASA) classification of physical status (Anesthesiologists, 2014). Patients were assigned one of the following points:

I A normally healthy patients

II A patient with mild systemic disease

III A patient with severe systemic disease

IV A patient with severe systemic disease that is a constant threat to life

V A moribund patient who is not expected to survive without the operation

VI A declared brain-dead patient whose organs are being removed for donor purposes

In this study, ASA status of III, IV and V were merged into one group indicating any score ≥ III.

Surgery related characteristics were as following:

Wound contamination

The American College of Surgeons determines four classes of surgical wound types based on the wound's level of contamination: clean, clean-contaminated, contaminated and dirty-infected. These classes allow health care professionals to better predict the risk of infections and wound healing outcomes. Detailed classification criteria for each class has been made into a table attached as Appendix 6. In this study, the variable wound contamination was simplified with two outcomes: clean versus all the others (clean-contaminated, contaminated and dirty-infected) due to the fact that primary hip arthroplasty was normally considered a clean wound surgery.

Duration of surgery

Duration of surgery was measured in minutes from surgery start time to finish time. Instead of using it as a continuous variable, it was grouped into four values: less than 60 minutes; 61 to 90 minutes; 91 to 120 minutes and more than 120 minutes.

NNIS risk index

The index value that ranges from 0 to 3 points is obtained from scoring one point when each of the following presents: (1) ASA physical status classification > II, (2) either contaminated or dirty/infected wound classification, (3) length of operation > T hours, where T is the approximate 75 percentile of the duration of the operation being performed.

Since NNIS risk index, by its definition, is obviously highly correlated with those three variables listed above, the estimation of this variable wound create multicollinearity. Therefore NNIS risk index categories were excluded from the multivariate analysis.

Elective surgery

This is a binary variable indicating whether the surgery was elective or not. It was coded as 0 and 1 representing emergency operation and elective operation respectively. Elective surgery is a surgery that is medically necessary, but can be delayed for at least 24 hours. Emergency operation on the other hand was a non-elective, unscheduled procedure where the standard immediate preoperative preparation that normally done within the facility was not allowed.

Perioperative antibiotic prophylaxis

It is the indicator of if antimicrobial therapy was used for the prevention of infection. And there were three categories: yes, no and unknown.

Cement

When the existing joint surface is replaced with artificial joint prostheses in the surgery, the orthopedic surgeon must make sure that the prostheses adhere to patient's natural bone. How this adhesion is achieved depends on what kind of prosthesis is used: a cemented joint prosthesis uses fast-drying bone cement to help fix it to the bone; a cement-less joint prosthesis allows the bone to grow onto it and adhere to it over time. This variable indicates whether a cemented joint prosthesis or a cement-less joint prosthesis or a hybrid prosthesis was used in each surgery.

Pre-operative stay

This is a continuous variable measuring the days patients spent in hospital before undergoing surgery.

Post-operative stay

It describes this time period from the moment when operation was finished to the time patient was discharged from hospital.

Follow-up time

The time period patients were followed up by hospitals, measured in day. Hospitals were required to follow each patient for 30 days after surgery and the NIPH requested a minimum of 80% post-discharge follow-ups from the hospitals (Løwer et al., 2013).

Additionally, there were another three independent variables describing hospital characteristics:

Hospital region

There are four geographical health care regions in Norway: South-Eastern, Western, Middle/Central and Northern (Appendix 1). Private hospital were categorized as "private" alongside the four health regions.

Type of hospital

Each hospital was categorized as one of the five types: primary, secondary, specialized, tertiary and unknown, according to the level of health care it provided.

Hospital size

Hospital size was measured using the number of hospital beds, and the three categories were large (>700), medium (301 to 700) and small (<300).

Considering that all independent variables chosen for this study had medical reasons for being of interest and the dataset was sufficiently large, therefore, all these independent variables except NNIS risk index were included in the multivariate logistic regression regardless of its significance in bivariate model. Odds ratio (OR), 95% confidence interval (CI) and *p*-value are provided for all the independent variables.

Data were analyzed using Stata®13 (Stata Corp., College Station, Texas) and a p-value < 0.05 was set as the statistical significance threshold.

3.4.2 Cost analysis

Michael F. Drummond and his colleagues identified the main categories of costs of health care programs as costs arising from the use of resources within the health sector; the resource use by patients and their families; the resource use in other sectors and productivity change (Drummond et al., 2005). In practice, the particular range of costs included in a given study is usually decided upon the viewpoint for the analysis and availability of data. Possible viewpoints of study include those of society, which is the broadest one, the health sector, the government in general, the hospital and the patient, etc. Specifying the viewpoint or perspective of the study is crucial because some items are costs from one point of view, but not costs from another point of view. Take the patient's transportation fee as an example: it is a cost from patient's point of view, but not a cost from a health sector perspective.

After the relevant range of costs being identified, each individual item must be measured and valued. That is, costing has two basic elements: measurement of the quantities of resource use (q) and the assignment of unit costs or prices (p) to each kind of resource (Drummond et al., 2005). Resource quantities could either be collected on the case report forms or be estimated by reviewing hospital records, depending on the context for the economic evaluation. With respect to the assignment of unit costs or prices, even though the theoretical true cost of using scarce healthcare resource is the value of the resource in its next best alternative use, or referred as "opportunity cost", the pragmatic approach is to use existing market prices unless particular reason suggesting otherwise (Drummond et al., 2005).

Costing can be time and effort consuming, so before proceeding to cost calculation, it is important for analysts to decide how accurate the costing need to be. In costing for hospital costs, there are four levels of precision, namely micro-costing, case-mix group, disease-specific *per diem* and average *per diem* (Drummond et al., 2005). When follow micro-costing, each resource component is identified and a unit cost assigned. Case-mix group (where diagnosis related groups fall into) gives the cost for each category of case and the other two give average daily cost. The other two give average daily cost in disease specific category or over all categories, making them the least precise.

Then the calculation of total cost requires the quantities of resource use (q) being multiplied by the unit costs (p) of the resources (Equation (1)).

In the present study, costs arising from the use of resources in hospital were estimated. The range of costs included in the analysis were costs of inpatient stay, outpatient clinic visits,

imaging examination, laboratory tests, pharmaceuticals and costs associated with readmissions due to SSI, if there was any.

Equation (1) could be rewritten as:

$$Total\ cost\ (TC) = q_{LOS} * p_{LOS} + q_{Read} * p_{Read} + q_{Reop} * p_{Reop} + q_{Out} * p_{Out} + q_{Ab} * p_{Ab} + q_{Pla} * p_{Pla} + q_{Xray} * p_{Xray} + q_{Arth} * p_{Arth} + q_{Blood} * p_{Blood} + q_{Bct} * p_{Bct} \quad (2)$$

Where LOS = length of stay, Read = readmission, Reop = reoperation, Out = outpatient clinic, Ab = antibiotics, Pla = plaster, Xray = X-ray examination, Arth = arthrocentesis, Blood = blood test, Bct = bacteriological test.

Data on quantities of resources used was collected through the orthopedic surgeon survey (**Table 3**).

Table 3 Quantities of health care resources used for treating SSI following primary hip arthroplasty in Norway*

Resources	**No infection**	**Superficial infection**	**Deep or Organ/Space infection**		
			DAIR or One-stage revision	**Two-stage revision**	**Resection**
Additional LOS	0	0.83	2.18	2.18	2.18
Readmission stay	0	0	14	21	14
Out-patient clinic visits	4	4	9	14	7
Wound care					
Plaster	3	3	8	13	13
Laboratory					
Blood test	0	0	14	20	14
Bacteriological test	0	0	6-9	11-17	6-9
X-ray investigation	6	6	6	6	4
Arthrocentesis	0	0	1	1	1
Reoperation					
Debridement and retention	0	0	1	NA	NA
One-stage revision	0	0	1	NA	NA
Two-stage revision	0	0	NA	1	NA

Resection	0	0	NA	NA	1
Antibiotics §					
Cefalotin	2g*4*1	2g*4*1	2g*4*1	2g*4*1	2g*4*1
Rimactan	0	0	300mg*2*90	0	0
Vancomicin	0	0	1g*2*7	1g*2*7	1g*2*7
Ciproxin	0	0	750mg*2*83	0	0
Ekvacillin	0	0	0	2g*4*7	2g*4*7
Diclocil	0	0	0	1g*4*76	1g*4*28

***** Based on information from one clinical expert except the data on prolonged length of stay (from the NOIS)
§ 2g*4*1 means 2g*4 dose per day for 1 day

As showed in **Table 4**, in lack of opportunity costs, I have used Norwegian DRG price list (unit cost NOK 41,462), SAMDATA report and the Norwegian Medicines Agency (Statens Legemiddelverk) database to estimate the unit cost of laboratory tests, inpatient stay, surgical treatment and pharmaceutical, etc. The cost of health personnel was not listed in the table because the average time health personnel spent on a single patient during the inpatient stay varied greatly based on individual surgeon or nurse; therefore, it was difficult for experts to measure in the survey. And more importantly, it was assumed to have been included in the cost of inpatient stay so it would be double-counted if listed separately.

Given the quantities of resources use and their unit costs, the total hospital cost was then calculated following equation (1).

Table 4 Unit cost of each kind of resource used in hospital for treating surgical site infection

Type of cost	Type of unit	Cost (NOK)	DRG number (Weight*****)	Source
Average cost per day in somatic hospital	Day	15,008*	NA	SAMDATA report 2013
Out-patient clinic	Visit	995	DRG908A (0.024)	DRG price list 2015
Wound care				
Plaster	Application of plaster	995	DRG908A (0.024)	DRG price list 2015
Laboratory tests				
Blood test	Test	10**	707a	Lovdata
Bacteriological test of wounds	Test	50***	704a	Lovdata
X-ray investigation	X-ray examination	130	RG2	Lovdata
Arthrocentesis	Number	1990	DRG808U (0.048)	DRG price list 2015

Reoperation				
Debridement and retention	Operation	92,543	DRG210N (2.232)	DRG price list 2015
One-stage revision	Operation	92,543	DRG210N (2.232)	DRG price list 2015
Two-stage revision/Replacement of hip prosthesis	Operation	225,056	DRG209C (5.428)	DRG price list 2015
Excision, in-patient	Operation	33,418	DRG230 (0.806)	DRG price list 2015
Excision, out-patient	Operation	13,309	DRG230O (0.321)	DRG price list 2015
Antibiotics ****				
Cefalotin	Pack (2g*10)	374	NA	Norwegian Medicines Agency
Rimactan	Pack (300mg*100)	437	NA	Norwegian Medicines Agency
Vancomycin	Pack (1g*1)	141	NA	Norwegian Medicines Agency
Ciproxin	Pack (750mg*100)	764	NA	Norwegian Medicines Agency
Ekvacillin	Pack (2g*10)	197	NA	Norwegian Medicines Agency
Diclocil	Pack (1g*5)	86	NA	Norwegian Medicines Agency

* NOK 14,638 in 2013, adjusted for inflation
** One test per visit
*** Five tests per visit
**** All prices are without VAT

3.5 Ethical consideration

Patient data were de-identified before the submission to the NIPH, so there was no identifiable individual level data contained in this thesis. Collection and use of NOIS data is governed by an own act NOIS-registerofrskriften. The project was approved by the PVO at the Norwegian Institute of Public Health (NIPH).

4 Results

4.1 Brief overview

Between September 2012 and December 2014, 53 hospitals contributed data on a total of 17,762 total hip arthroplasty operations while 46 hospitals reported data on 7334 hemiarthroplasty procedures. From the day of surgery to 30 days afterwards, 390 (2.2%) total hip arthroplasty patients and 264 (3.6%) of hemiarthroplasty patients were diagnosed with SSIs. Of all the 390 infection cases after total hip arthroplasty, 206 (53%) were superficial and 184 (47%) were deep or organ/space infections, while for hemiarthroplasty infections, the number of superficial infection was 113 (43%) and 151 (57%) were deep or organ/space infections.

4.2 Descriptive statistics on central variables

4.2.1 Total hip arthroplasty (THA)

4.2.1.1 Patient characteristics

The majority of arthroplasty patients (n=11,593) were females, making up to 65% of the study population while 6169 (35%) were males. Compared with male patients, female patients had a lower proportion of infection (2.0% *vs*. 2.6%, $p < 0.01$). The overall mean age for THA patients was 68 years (SD 11.1). Patients with SSI were 1.4 years older than those without ($p = 0.01$). With respect to ASA score, patients with a score higher than or equal to III had a higher risk of acquiring infection (3.9% *vs*. 1.8%, $p < 0.01$) comparing with those had an ASA score of I and II.

Table 5 Characteristics of total hip arthroplasty (THA) patients in Norway between September 2012 and December 2014, by surgical site infection (SSI) status.

Variable	Not infected (n=17372)	Infected (n=390)	Total (N=17762)	*p*-value
Age (yrs)				
Mean (SD)	68.0 (11.1)	69.4 (11.2)	68.0 (11.1)	0.01
Median	69	70	69	
Min, Max	11, 102	23, 96	11, 102	
Sex				
Male	6009 (97.4 %)	160 (2.6 %)	6169 (100 %)	< 0.01
Female	11363 (98.0 %)	230 (2.0 %)	11593 (100 %)	
ASA category				
I and II	13850 (98.2 %)	258 (1.8 %)	14108 (100 %)	< 0.01
≥ III	3103 (96.1 %)	125 (3.9 %)	3228 (100 %)	
Missing	419 (98.4 %)	7 (1.6 %)	426 (100 %)	

4.2.1.2 Surgery characteristics

A greater proportion of infected patients was found among patients with a higher-than-1 NNIS risk index than among those with an index of 0 or 1 (4.6% *vs*. 2.1%, $p < 0.01$). 2.8% of the surgeries where prosthesis was fixed without cement were infected within 30 days after surgery while for surgeries using cement or hybrid fixation the infection proportion was 2% (Table 6). On average, THA patients stayed in hospital for 4.1 days (range 0-340, SD 4.6) after surgery. Infected patients stayed longer (5.6 days, range 0-107, SD 8.5) at hospital after surgery than those without infection (4.1 days, range 0-340, SD 4.5) ($p < 0.01$).

Table 6 Surgery characteristics of total hip arthroplasty (THA) in Norway between September 2012 and December 2014, by surgical site infection (SSI) status

Variable	Not infected (n=17372)	Infected (n=390)	Total (N=17762)	*p*-value
Wound contamination				
Clean	16862 (97.8 %)	373 (2.2 %)	17235 (100 %)	0.18
Other	112 (95.7 %)	5 (4.3 %)	117 (100 %)	
Missing	398 (97.1 %)	12 (2.9 %)	410 (100 %)	
Duration of surgery (min)				
< 60	2729 (98.3 %)	48 (1.7 %)	2777 (100 %)	0.15
61 to 90	7543 (97.7 %)	175 (2.3 %)	7718 (100 %)	
91 to 120	4683 (97.9 %)	99 (2.1 %)	4782 (100 %)	
>120	2221 (97.2 %)	63 (2.8 %)	2284 (100 %)	
Missing	196 (97.5 %)	5 (2.5 %)	201 (100 %)	
NNIS risk index				
0 or 1	16224 (97.9%)	348 (2.1%)	16572 (100%)	< 0.01
2 or 3	515 (95.4%)	25 (4.6%)	540 (100%)	
Missing	633 (97.4%)	17 (2.6%)	650 (100%)	
Elective surgery				
Yes	16175 (97.8%)	370 (2.2%)	16545 (100%)	0.22
No	1161 (98.3%)	20 (1.7%)	1181 (100%)	
Peri-operative prophylaxis§				
Yes	16041 (97.9%)	384 (2.1%)	16389 (100%)	0.07
No	482 (97.0%)	15 (3.0%)	497 (100%)	
Unknown	838 (96.9%)	27 (3.1%)	865 (100%)	
Cement				
Yes	5342 (98.0%)	111 (2.0%)	5453 (100%)	< 0.01
No	4534 (97.2%)	129 (2.8%)	4663 (100%)	
Hybrid	7496 (98.0%)	150 (2.0%)	7646 (100%)	
Pre-operation stay (day)				
Mean (SD)	0.85 (1.2)	0.83 (1.2)	0.85 (1.2)	0.13
Median	1.0	1.0	1.0	
Min, Max	0, 51	0, 13	0, 51	
Post-operation stay (day)				
Mean (SD)	4.10 (4.5)	5.57 (8.5)	4.14 (4.6)	< 0.01
Median	3.0	4.0	3.0	
Min, Max	0, 340	0, 107	0, 340	

4.2.1.3 Hospital characteristics

Three variables, hospital region, type of hospital and number of hospital beds, were used to describe hospitals.

As illustrated in **Table 7**, despite that only 7% of the procedures were done in hospitals that belonged to the Northern Norway Regional Health Authority (Helse Nord RHF), they had the highest proportion of infection (3.7% (45 out of 1207)). Followed by those performed by Middle/Central Norway Regional Health Authority (Helse Midt RHF) (3.1% (82 of 2650)), hospitals in South-Eastern Norway Regional Health Authority (Helse Sør-Øst RHF) (2.4% (172 of 7061)), then those in the Western Norway Regional Health Authority (Helse Vest RHF) (1.8% (50 of 2833)), and finally private hospitals (1.0% (41 of 4011)).

Infection proportions among the four hospital types were also significantly different. In specialty hospitals only 0.5% (11 of 2163) of THAs were infected whereas in the other types of hospitals (primary, secondary and tertiary) about 2.5% of the surgeries were reported as infected.

Table 7 Hospital characteristics of total hip arthroplasty (THA) in Norway between September 2012 and December 2014, by surgical site infection (SSI) status

Variable	Not infected (n=17372)	Infected (n=390)	Total (N=17762)	*p*-value
Hospital region				
Middle	2568 (96.9 %)	82 (3.1%)	2650 (100%)	< 0.01
Northern	1162 (96.3 %)	45 (3.7%)	1207 (100%)	
South-Eastern	6889 (97.6 %)	172 (2.4%)	7061 (100%)	
Western	2783 (98.2 %)	50 (1.8%)	2833 (100%)	
Private	3970 (99.0 %)	41 (1.0%)	4011 (100%)	
Type of hospital				
Primary	7574 (97.5%)	192 (2.5%)	7766 (100%)	< 0.01
Secondary	4067 (97.6%)	102 (2.5%)	4169 (100%)	
Specialty	2152 (99.5%)	11 (0.5%)	2163 (100%)	
Tertiary	2834 (97.5%)	72 (2.5%)	2906 (100%)	
Unknown	745 (98.3%)	13 (1.7%)	758 (100%)	
Number of hospital beds				
0 to 300	10994 (98.0%)	230 (2.1%)	11224 (100%)	0.12
301 to 700	4455 (97.4%)	118 (2.6%)	4573 (100%)	
> 700	1923 (97.9%)	42 (2.1%)	1965 (100%)	

4.2.2 Hemiarthroplasty (HA)

4.2.2.1 Patient characteristics

The mean age of patients who underwent hemiarthroplasty during the study period was 83 years (SD 8.4); making them almost 15 years older than total hip arthroplasty patients. The proportion of females was 71% (5199 out of 7334). Male patients had a higher risk of infection than female

ones (4.9% *vs* 3.1%, $p < 0.01$). As for ASA scores, patients with a score ≥ III doubled the infection proportion when compared with those with score I and II (4.4% *vs*. 2.2%, $p < 0.01$).

Table 8 Characteristics of hemiarthroplasty (HA) patients in Norway between September 2012 and December 2014, by surgical site infection (SSI) status

Variable	Not infected (n=7070)	Infected (n=264)	Total (N=7334)	*p*-value
Age (yrs)				
Mean (SD)	82.7 (8.4)	82.2 (8.4)	82.7 (8.4)	0.40
Median	84	83	84	
Min,Max	16,102	44,98	16,102	
Sex				
Male	2031 (95.1%)	104 (4.9%)	2135 (100%)	< 0.01
Female	5039 (96.9%)	160 (3.1%)	5199 (100%)	
ASA category				
I and II	2596 (97.8%)	59 (2.2%)	2655 (100%)	< 0.01
≥ III	4350 (95.6%)	201 (4.4%)	4551 (100%)	
Missing	124 (96.9%)	4 (3.1%)	128 (100%)	

4.2.2.2 Surgery characteristics

In Norway, more than 80% of hemiarthroplasties performed during study period were emergency procedures that lasted less than 2 hours. Generally, patients spent 1.1 days in hospital before the surgery and another 5.2 days afterwards. Perioperative antibiotic prophylaxis was administered in 92% of the operations and 71% of the procedures used cemented component for prosthesis fixation.

However, no statistically significant difference in infection proportions according to the surgery characteristics listed in **Table 9** was found.

Table 9 Surgery characteristics of hemiarthroplasty in Norway between September 2012 and December 2014, by surgical site infection (SSI) status

Variable	Not infected (n=7070)	Infected (n=264)	Total (N=7334)	*p*-value
Wound contamination				
Clean	6898 (96.4%)	259 (3.6%)	7157 (100%)	0.60
Other	67 (95.7%)	3 (4.3%)	70 (100%)	
Missing	105 (98.1%)	2 (1.9%)	107 (100%)	
Duration of surgery (min)				
< 60	1764 (96.6%)	62 (3.4%)	1826 (100%)	0.94
61 to 90	3247 (96.5%)	119 (3.5%)	3366 (100%)	
91 to 120	1476 (96.1%)	60 (3.9%)	1536 (100%)	
> 120	537 (96.2%)	21 (3.8%)	558 (100%)	
Missing	46 (95.8%)	2 (4.2%)	48 (100%)	
NNIS risk index				
0 or 1	6542 (96.5%)	241 (3.6%)	6783 (100%)	0.10
2 or 3	334 (94.6%)	19 (5.4%)	353 (100%)	
Missing	194 (98.0%)	4 (2.0%)	198 (100%)	
Elective surgery*				
Yes	868 (96.4%)	32 (3.6%)	900 (100%)	0.94
No	6200 (96.4%)	232 (3.6%)	6432 (100%)	
Peri-operative prophylaxis§				
Yes	6479 (96.4%)	241 (3.6%)	6720 (100%)	0.57
No	103 (98.1%)	2 (1.9%)	105 (100%)	
Unknown	477 (96.0%)	20 (4.0%)	497 (100%)	
Cement				
Yes	5022 (96.5%)	182 (3.5%)	5204 (100%)	0.46
No	2048 (96.2%)	82 (3.9%)	2130 (100%)	
Pre-operation stay (day)				
Mean (SD)	1.10 (1.7)	1.09 (1.4)	1.1 (1.7)	0.38
Median	1.0	1	1	
Min,Max	0,60	0,12	0,60	
Post-operation stay (day)				
Mean (SD)	5.17 (5.3)	6.66 (8.4)	5.22 (5.4)	0.41
Median	4.0	4.0	4.0	
Min, Max	0, 158	0, 53	0, 158	

* n = 7332

§ n = 7322

4.2.2.3 Hospital characteristics

Patients in Northern Norway (Helse Nord RHF) hospitals had the highest infection risk while patients operated in private ones had the lowest. When sorted by type, most of the hospitals had

an infection percentage between 3%-4%, whereas specialty hospitals had an infection proportion of 0% (0 out of 3). The difference, however, was not significant due to limited patient number in specialty hospital. The number of hospital beds seemed to be positively associated with infection, but the association was not statistically significant.

Table 10 Hospital characteristics of hemiarthroplasty in Norway between September 2012 and December 2014, by surgical site infection (SSI) status

Variable	Not infected (n=7070)	Infected (n=264)	Total (N=7334)	*p*-value
Hospital region				
Middle	1018 (95.7%)	46 (4.3%)	1064 (100%)	0.07
North	564 (95.0%)	30 (5.1%)	594 (100%)	
South-east	3775 (96.5%)	139 (3.6%)	3914 (100%)	
West	1098 (97.1%)	33 (2.9%)	1131 (100%)	
Private	615 (97.5%)	16 (2.5%)	631 (100%)	
Type of hospital				
Primary	3169 (96.8%)	105 (3.2%)	3274 (100%)	0.51
Secondary	2090 (96.3%)	81 (3.7%)	2171 (100%)	
Specialty	3 (100%)	0 (0)	3 (100%)	
Tertiary	1723 (95.9%)	74 (4.1%)	1797 (100%)	
Unknown	85 (95.5%)	4 (4.5%)	89 (100%)	
Number of hospital beds				
0 to 300	3388 (96.7%)	114 (3.3%)	3502 (100%)	0.18
301 to 700	2646 (96.3%)	102 (3.7%)	2748 (100%)	
> 700	1036 (95.6%)	48 (4.4%)	1084 (100%)	

4.3 Results from logistic regression

The bivariate and multivariate associations of each of the possible risk factors investigated with infection status are shown in **Table 11** (THA) and **Table 12** (Hemiarthroplasty).

4.3.1 Risk factors for SSI after THA

In bivariate regression, the variables that were associated with higher risk of developing surgical site infections after THA were age, male gender, ASA score ≥ III, surgery lasting longer than 120 minutes, NNIS risk index > 1, cement-less fixation, post-operative hospital stay and medium size hospital (hospitals with 301 to 700 beds) (**Table 11**). Those associated with lower infection risk were private hospital, public hospitals that belonged to the Western Norway Regional Health Authority (Helse Vest RHF) and specialty hospital. Variables such as wound contamination, elective surgery, perioperative antibiotic prophylaxis, pre-operation stay,

though not significantly associated with infection in the bivariate analysis, were also included in the multivariate model due to their clinical importance.

The multivariate model showed the independent risk factors for SSI while adjusting for other risk factors. According to the multivariate model, the odds of developing surgical site infection for males were 1.27 (95% CI 1.03 to 1.56; $p = 0.03$) times greater than for females. The risks of surgical site infection varied according to the duration of surgery, with the greatest risk for procedures that lasted more than 120 minutes (OR 1.78, compared with the ones < 60 minutes). Although only 26% of the THAs used cement-less component for prosthesis fixation, their infection risk was 84% higher than that for cemented procedures. In addition, patients undergoing elective total hip arthroplasty procedures were 1.87 times (95% CI 1.17 to 3.00, $p < 0.01$) more likely to have SSI compared with those undergoing non-elective ones.

The odds of developing surgical site infection when perioperative antibiotic prophylaxis was administered were 0.51 (95% CI: 0.28 to 0.93) times as the odds when it was not used. For the Western Norway RHA (Helse Vest RHF) hospitals, the risk of surgical site infection were 40% (OR 0.6, $p = 0.02$) lower than that for hospitals belonged to the Middle/Central Norway RHA (Helse Midt RHF); and for private hospitals the infection risk was only 0.36 times as that for middle/central RHA hospitals (OR 0.36, $p < 0.01$). Furthermore, the odds of infection in specialty hospital were 66% (OR 0.34, $p < 0.01$) less than in primary hospitals.

After adjusting for other variables, elective surgery and no perioperative antibiotic prophylaxis became risk factors for SSIs while the number of hospital beds between 301 and 700 was no longer one.

Table 11 Risk factors for developing SSI after THA, Norway, between September 2012 and December 2014

	Bivariate			**Multivariate**		
	Odds ratio	**95 % CI§**	***p*-value**	**Odds ratio**	**95 % CI§**	***p*-value**
Patient characteristics						
Age (1-year increment)	1.01	1.00 to 1.02	0.01	1.01	1.00 to 1.02	0.02
Gender						
Female	1.00	Baseline		1.00	Baseline	
Male	1.32	1.07 to 1.61	0.01	1.27	1.03 to 1.56	0.03
ASA score						
1 and 2	1.00	Baseline		1.00	Baseline	
≥3	2.16	1.74 to 2.69	< 0.01	1.87	1.48 to 2.36	< 0.01
Missing	0.90	0.42 to 1.91	0.78	0.45	0.11 to 1.86	0.27
Procedure characteristics						

Wound contamination						
Clean	1.00	Baseline		1.00	Baseline	
Other	2.02	0.82 to 4.97	0.13	2.07	0.83 to 5.14	0.12
Missing	1.36	0.76 to 2.44	0.30	1.65	0.80 to 3.41	0.18
Duration of surgery (minutes)						
< 60	1.00	Baseline		1.00	Baseline	
61 to 90	1.32	0.96 to 1.82	0.09	1.35	0.96 to 1.90	0.09
91 to 120	1.20	0.85 to 1.70	0.30	1.31	0.89 to 1.92	0.17
> 120	1.61	1.10 to 2.36	0.01	1.78	1.16 to 2.73	< 0.01
Missing	1.45	0.57 to 3.68	0.43	1.92	0.35 to 10.65	0.45
Elective surgery						
No	1.00	Baseline		1.00	Baseline	
Yes	1.33	0.84 to 2.09	0.22	1.87	1.17 to 3.00	< 0.01
Perioperative prophylaxis						
No	1.00	Baseline		1.00	Baseline	
Yes	0.70	0.41 to 1.18	0.18	0.51	0.28 to 0.93	0.03
Unknown	1.04	0.55 to 1.97	0.92	0.92	0.47 to 1.81	0.81
Cement						
Yes	1.00	Baseline		1.00	Baseline	
No	1.37	1.06 to 1.77	0.02	1.84	1.35 to 2.51	< 0.01
Hybrid	0.96	0.75 to 1.23	0.77	1.24	0.93 to 1.65	0.15
Pre-operation stay (days)						
≤1	1.00	Baseline		1.00	Baseline	
>1	1.07	0.78 to 1.46	0.68	1.32	0.95 to 1.84	0.10
Post-operation stay (days)	1.02	1.01 to 1.03	< 0.01	1.02	1.01 to 1.03	< 0.01
Hospital characteristics						
Hospital region						
Middle	1.00	Baseline		1.00	Baseline	
North	1.21	0.84 to 1.76	0.31	0.99	0.65 to 1.52	0.98
South-east	0.78	0.60 to 1.02	0.07	0.77	0.56 to 1.06	0.11
West	0.56	0.39 to 0.80	< 0.01	0.60	0.39 to 0.92	0.02
Privat	0.32	0.22 to 0.47	< 0.01	0.36	0.23 to 0.54	< 0.01
Type of hospital						
Primary	1.00	Baseline		1.00	Baseline	
Secondary	0.99	0.78 to 1.26	0.93	0.99	0.55 to 1.75	0.96
Specialty	0.20	0.11 to 0.37	< 0.01	0.34	0.18 to 0.66	< 0.01
Tertiary	1.00	0.76 to 1.32	0.99	1.42	0.68 to 2.95	0.35
Unknown	0.69	0.39 to 1.21	0.20	0.63	0.34 to 1.17	0.14
Number of hospital beds						
0 to 300	1.00	Baseline		1.00	Baseline	
301 to 700	1.27	1.01 to 1.58	0.04	0.76	0.42 to 1.37	0.36
> 700	1.04	0.75 to 1.46	0.80	0.47	0.21 to 1.07	0.07
NNIS risk index						
0 or 1	1.00	Baseline		-##	-	-

2 or 3	2.26	1.49 to 3.43	< 0.01	-	-	-
Missing	1.25	0.76 to 2.05	0.37	-	-	-

§ Confidence Interval ## Variable excluded because of multicollinearity

4.3.2 Risk factors for SSI after HA

For hemiarthroplasty, male sex, ASA score ≥ III and longer post-operation stay were significant risk factors for SSIs, whereas in multivariate analysis, cement-less surgery was also identified as an additional risk factor (**Table 12**). The infection risks were significantly greater for male patients as well as for those with an ASA score ≥ III, when compared with their counterparts (OR 1.45 for male, OR 1.91 for ASA score ≥ III, $p < 0.01$). In cement-less HAs the infection risk was 45% higher (OR 1.45, $p = 0.02$) than in those used cement. The risk of surgical site infection increased significantly yet slightly (OR 1.02, $p < 0.01$) with length of post-operative hospital stay. There were no significant associations between the risk of infection after hemiarthroplasty procedures and duration of surgery, perioperative antibiotic prophylaxis, NNIS risk index as well as any of the hospital characteristics.

Table 12 Risk factors for SSI after hemiarthroplasty, Norway, between September 2012 and December 2014

	Bivariate			**Multivariate**		
	Odds ratio	**95% CI**	***p*-value**	**Odds ratio**	**95% CI**	***p*-value**
Patient characteristics						
Age (1-year increment)	0.99	0.98 to 1.01	0.40	0.99	0.98 to 1.01	0.32
Gender						
Female	1.00	Baseline		1.00	Baseline	
Male	1.61	1.25 to 2.08	< 0.01	1.45	1.12 to 1.87	< 0.01
ASA score						
I and II	1.00	Baseline		1.00	Baseline	
≥ III	2.03	1.51 to 2.73	< 0.01	1.91	1.41 to 2.59	< 0.01
Missing	1.42	0.51 to 3.97	0.51	1.20	0.30 to 4.86	0.79
Procedure characteristics						
Wound contamination						
Clean	1.00	Baseline		1.00	Baseline	
Other	1.19	0.37 to 3.82	0.77	0.98	0.30 to 3.18	0.97
Missing	0.51	0.12 to 2.07	0.34	0.52	0.11 to 2.53	0.42
Duration of surgery (minutes)						
< 60	1.00	Baseline		1.00	Baseline	
61 to 90	1.04	0.76 to 1.43	0.79	1.07	0.75 to 1.46	0.69
91 to 120	1.16	0.81 to 1.66	0.43	1.18	0.78 to 1.72	0.42
> 120	1.11	0.67 to 1.84	0.68	1.18	0.67 to 1.95	0.54
Missing	1.24	0.29 to 5.21	0.77	2.94	0.33 to 15.20	0.29
Elective surgery						

No	1.00	Baseline		1.00	Baseline	
Yes	0.99	0.68 to 1.44	0.94	0.96	0.63 to 1.46	0.85
Perioperative prophylaxis						
No	1.00	Baseline		1.00	Baseline	
Yes	1.92	0.47 to 7.81	0.37	1.87	0.45 to 7.80	0.39
Unknown	2.16	0.50 to 9.38	0.30	1.77	0.39 to 7.99	0.46
Cement						
Yes	1.00	Baseline		1.00	Baseline	
No	1.10	0.85 to 1.44	0.46	1.45	1.05 to 1.99	0.02
Pre-operation stay (days)						
≤1	1.00	Baseline		1.00	Baseline	
>1	1.00	0.73 to 1.37	0.99	0.89	0.65 to 1.23	0.49
Post-operation stay (days)	1.03	1.01 to 1.04	< 0.01	1.02	1.01 to 1.04	< 0.01
Hospital characteristics						
Hospital region						
Middle	1.00	Baseline		1.00	Baseline	
North	1.18	0.73 to 1.89	0.50	1.39	0.81 to 2.39	0.23
South-east	0.81	0.58 to 1.15	0.24	0.99	0.65 to 1.49	0.95
West	0.67	0.42 to 1.05	0.08	0.62	0.37 to 1.03	0.07
Privat	0.58	0.32 to 1.03	0.06	0.66	0.34 to 1.26	0.21
Type of hospital						
Primary	1.00	Baseline		1.00	Baseline	
Secondary	1.17	0.87 to 1.57	0.30	1.04	0.41 to 2.65	0.94
Specialty	1.00	-	-	1.00	-	-
Tertiary	1.30	0.96 to 1.76	0.09	0.86	0.30 to 2.50	0.79
Unknown	1.42	0.51 to 3.94	0.50	1.55	0.53 to 4.58	0.42
Number of hospital beds						
0 to 300	1.00	Baseline		1.00	Baseline	
301 to 700	1.15	0.87 to 1.50	0.33	1.10	0.43 to 2.82	0.85
> 700	1.38	0.98 to 1.94	0.07	1.99	0.62 to 6.41	0.25
NNIS risk index						
0 or 1	1.00	Baseline		-	-	-
2 or 3	1.54	0.96 to 2.50	0.08	-	-	-
Missing	0.56	0.21 to 1.52	0.26	-	-	-

4.4 Results of cost analysis

The costs incurred in hospital after initial hip arthroplasty sorted by infection status is shown in Table 13. Patients without infection had a post-operative cost of NOK 7,895 comprising the cost of outpatient clinic visit, application of plaster, x-ray examination and antibiotics. Compared with non-infected patients, patients with superficial infections spent 2.8 days more in hospital after surgery, leading to a higher post-operative cost of NOK 20,352. Costs of the most severe infections varied from NOK 303,775 to NOK 611,380 according to the

management strategy applied. After incorporating management strategy frequencies, the overall average post-operative cost for patients with deep or organ/space infection was NOK 415,382, mainly due to a substantial increase in resource use e.g. readmission and reoperation.

Table 13 Postoperative hospital cost by infection status after primary hip arthroplasty in Norway, between September 2012 and December 2014, measured in 2015 Norwegian krone

	No infection	**Superficial infection**	**Deep or Organ/Space infection**		
Cost component			DAIR* or One-stage revision	Two-stage revision	Resection
Additional LOS	0	12,457	32,717	32,717	32,717
Readmission	0	0	210,112	315,168	210,112
Reoperation	0	0	92,543	225,056	33,418
Outpatient clinic	3,980	3,980	8,955	13,930	6,965
Antibiotics	150	150	4,178	7,904	4,602
Plaster	2,985	2,985	7,960	12,935	12,935
X-ray	780	780	780	780	520
Arthrocentesis	0	0	1,990	1,990	1,990
Blood test	0	0	140	200	140
Bacteriological test	0	0	375	700	375
Total	7,895	20,352	359,751	611,380	303,775
			415,382		

* DAIR: Debridement and implant retention

With these costs being given, the attributable cost due to surgical site infection could then be calculated (**Table 14**). The mean hospital cost for treating a superficial infection was NOK 12,457, arising from additional length of stay. Similar to the post-operative costs, the attributable SSI costs for deep or organ/space infections varied with revision procedures. That is, infections treated with DAIR or one-stage exchange had an attributable hospital cost of NOK 351,856 while those treated with two-stage revisions caused a much higher cost of NOK 603,485 and the remaining infections treated with resection prosthesis had a lower hospital cost of NOK 295,880. After accounting for the proportions of each revision procedure in Norway, the overall cost of a deep or organ/space infection for hospital was NOK 407,487.

Table 14 Costs attributable to SSI by infection status after primary hip arthroplasty in Norway between September 2012 and December 2014, measured in 2015 Norwegian krone

	No infection	**Superficial infection**	**Deep or Organ/Space infection**		
			DAIR or One-stage revision	Two-stage revision	Resection
Attributable cost due to SSI	0	12,457	351,856	603,486	295,880
			407,487		

Despite of the big cost difference between superficial infection (NOK 12,457) and deep or organ/space infection (NOK 407,487), their proportions in the infection group were similar (superficial infection: 53%; deep or organ/space infection: 47%). Therefore, when emerging the two infection groups into a new one that indicated the existence of SSI, the overall cost was balanced to NOK 198,121 (Table 15).

Table 15 Post-operative hospital cost and attributable cost due to SSI sorted by No SSI/SSI after primary hip arthroplasty in Norway between September 2012 and December 2014, measured in Norwegian Krone

	No SSI	SSI
Hospital cost after initial surgery	7,895	206,016
Attributable cost due to SSI	0	198,121

A cost breakdown was shown in **Figure 7** to identify the most important cost drivers for SSI. More than half (56%) of the hospital costs for treating a SSI was incurred by subsequent inpatient stay (readmission to hospital) and 28% came from surgical revision procedures (reoperation). Together these two components constituted more than 80% of the SSI cost for hospital. The third important cost component was prolonged hospital stay (11%) after the initial hip arthroplasty. Other cost items, such as plaster (2%), antibiotics (1%), outpatient clinic (1%), were minor ones that could hardly change the total cost on a great scale.

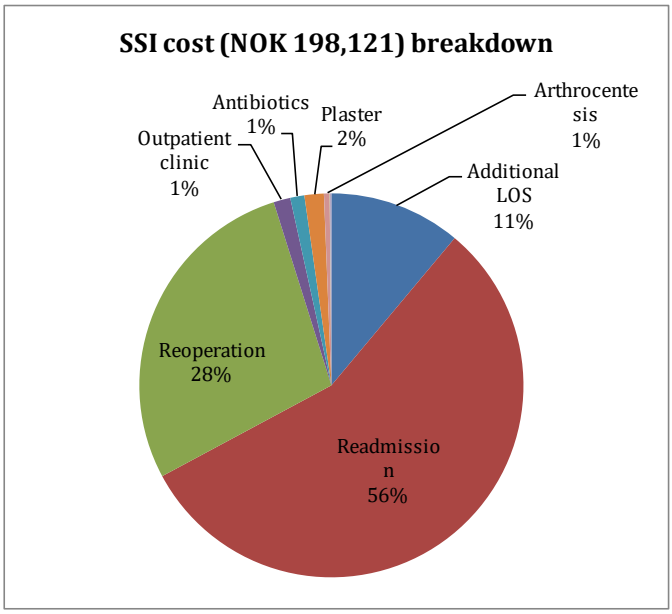

Figure 7 SSI cost after primary hip arthroplasty in Norway between September 2012 and December 2014 according to cost component

5 Discussion

5.1 Main findings and implications

5.1.1 Risk factor analysis

The overall incidence rate of SSIs following total hip arthroplasty (THA) in a cohort of 17,762 cases monitored within NOIS was 2.2%. This is similar to that reported from the Surgical Site Infection Surveillance Service (SSISS) in England with 16,291 cases (S. Ridgeway et al., 2005) but lower than the 1-year incidence (3.0%) observed in NOIS among 5,540 cases from 2005-2009 (Dale et al., 2011). This could be related to the relatively short follow-up period in NOIS after THA that failed to capture the infections diagnosed later than 30 days after surgery. Alternatively, it could be an effect of having a surveillance system as it has been shown by others (Wilson et al., 2006) that having surveillance lead to lower SSI risk.

This study evaluated the association of patient characteristics, as well as procedure and hospital characteristics with SSIs after THA and HA. Male sex, cement-less fixation and post-operative hospital stay were risk factors that common to both SSIs after THA and those after HA.

Patient-related risk factors for SSI after THA included age, sex and ASA score. Although sex is among one of the most frequently detected risk factors for SSI after THA, its influence appears to be contradictory in the literature. In our study, male sex had an increased risk of infection compared with its female counterparts. The same finding was reported in another Norwegian study (Dale et al., 2011) from 2011, although the result was not statistically significant. Similarly, investigators in the United States using the National Inpatient Sample (NIS) data found that the risk of infection for men was 33% higher than that for women (OR = 1.33) (Poultsides et al., 2013). In contrast, another US study using joint replacement registry data claimed men to have a hazard ratio of 0.70 (Namba et al., 2012 October) and a lower risk of infection in male patients was also been found by Dutch researchers (Muilwijk, Walenkamp, Voss, Wille, & van den Hof, 2006). The difference of gender effect on SSI might be associated with the different underlying physical conditions of both sexes in the country where the study was carried out. In Norway, the diabetes mellitus prevalence for men was higher than that for women (9.0% *vs.* 5.1%) (Jenum et al., 2003). And diabetes have been documented as risk factor for SSI in a number of studies (Triantafyllopoulos, Stundner, Memtsoudis, & Poultsides, 2015). Therefore, a higher risk of SSI for male patients may resulted from the higher risk of diabetes for Norwegian men. That is, instead of by itself, the gender effect on SSI risk was due to confounder (diabetes) that was not included in the model. In addition, some researchers

suggested in their study (Willis-Owen, Konyves, & Martin, 2010) that this could be accounted for by gender differences in skin microbial colonization.

ASA score is an approximate reflection of patient's general physical status where a higher score indicates a worse physical status. Compared to patients with ASA score of I and II, we observed a risk of 1.87 (95% CI 1.48 to 2.36, $p < 0.01$) for patients with an ASA score ≥ III. This positive correlation of ASA score and infection risk after THA is in accordance with previously published findings (Dale et al., 2011; Namba et al., 2012 October; S. Ridgeway et al., 2005).

Another predictor of the risk of SSI was the prolonged duration of surgery. Compared to surgeries that lasted less than 60 minutes, the infection risk increased significantly in procedures that lasted for 120 minutes or more. As S. Ridgeway and colleagues (S. Ridgeway et al., 2005) suggested in their study, the prolonged duration of surgery perhaps served as a marker for "more complex surgery, in which existed a combination of prolonged surgical exposure and tissue damage during the procedure" and diminished efficacy of antibiotic prophylaxis, which could make these surgeries more susceptible to infection.

Other surgical characteristics associated with higher risk of infection were elective surgery, cement-less prosthesis and post-operation stay. Besides, the use of perioperative antibiotic prophylaxis was associated with lower risk of infection.

Although 93% (16545 of 17762) of THAs were elective surgery, compared with emergency surgery, it had a higher risk of infection. To my knowledge, no similar finding was reported in previous studies. This might be a result of some confounder that was not included in the regression model, such as bearing surface, bilateral procedures, etc. Further study needs to be done to find out the real reason. According to the Norwegian Arthroplasty Register (T. N. A. Register, 2010), nearly all cemented total hip arthroplasties performed in Norway were inserted with cement containing antibiotics. Protected both systemically by perioperative antibiotic prophylaxis and locally by the antibiotic eluted from cement, cemented hip prosthesis was consequently less likely to be infected compared to cement-less ones.

Perioperative antibiotic prophylaxis is a commonly reported indicator of lower infection risk in both the current and previous studies (Triantafyllopoulos et al., 2015) and it is also a standard practice for THA. However, despite improved antibiotic prophylaxis, in recent years, an increasing incidence of infection after THA was reported in both Norway and other Nordic countries (Dale et al., 2012; Dale et al., 2009). Researchers believed that this was an actual

increase since no change in risk factors could account for it. And the real reasons for this increase were not evident.

Unlike previous investigators identifying pre-operation stay as a risk factor for infection (Muilwijk et al., 2006; S. Ridgeway et al., 2005); it was not found to be an independent risk factor in the current analysis both before and after adjusting for other factors.

It is not a common practice to include hospital characteristics in risk analysis models. An American study by R. S. Namba et al. (Namba et al., 2012 October), however, included hospital volume as one of the possible risk factors for surgical site infection, but no significant association between this factor and the risk of infection was found. In this study, both private hospitals and public hospitals that belonged to the Western Norway Regional Health Authority (Helse Vest RHF) showed lower risks of infection compared with hospitals belonged to the Middle/Central Norway Regional Health Authority (Helse Midt RHF). Additionally, compared to primary hospitals, the risk of developing surgical site infection for patients in specialty hospitals was significantly lower. These findings may indicate that there are considerable heterogeneities concerning the adherence to optimal guideline, surgeon experience, hospital infection control policy, etc. among different hospital regions and hospital types.

Of all the risk factors for SSI, modifiable ones could be of interest for the design and implementation of preventive interventions to reduce infection rate. Based on the statistical results from the current study, perioperative antibiotic prophylaxis and cement fixation are recommended procedures for controlling SSIs. In Norway, however, they have been practicing for a long time (N. A. Register, 2015). This finding indicates that further studies in search of interventions to prevent SSI should focus on analyzing the effect of various parameters of perioperative antibiotic prophylaxis and cemented fixation, such as the time, route and dosage of administration, etc.

It should be considered to include more surgery related and hospital related factors, such as primary diagnosis, skin preparation and bilateral procedures, in the NOIS dataset. It would be a helping hand in both estimating factor effect more accurately and establishing more practical and specific SSI prevention guidelines.

5.1.2 Cost analysis

The economic burden of SSI for Norwegian hospitals was high. The mean hospital cost of an SSI estimated in this study was NOK 198,121, incorporating a superficial infection cost of NOK

12,457 and deep or organ/space infection cost of NOK 407,487. Patients who developed an SSI on average spent 18 more days in hospital compared with those without infection, mainly due to readmission to hospital (15.2 days). The most important cost drivers for SSI identified in this study were subsequent inpatient stay (56%), revision surgery (28%) and prolonged initial length of stay (11%). The results of this study indicate that the additional cost for superficially infected patients was the result of prolonged stay in hospital and that for severely infected patients was largely due to revision procedure and re-hospitalization. These findings support the hypothesis regarding the cost drivers for SSI treatment.

Since no study had examined the economic impact of SSI after hip arthroplasty for Norwegian hospitals before, direct comparison with other studies could not be carried out. Unlike the risk factor analysis, cost findings reported by previous researchers varied considerably due to inconsistencies in research methods, health care system settings, cost components included and perspectives adopted, etc. and one should be cautious about comparing them without any further analysis.

A UK study (Jenks et al., 2014) yielded a median cost attributable to SSI following hip replacement of GBP 3,214 (NOK 43,235) while C. Edwards et al. (2008) claimed in their study that the mean cost for treating an infected patient was GBP 25,940 (NOK 419,853). A plausible explanation for the huge difference in these two cost estimations could be the heterogeneity in infection severity, type of revision surgery and inclusion of readmission.

The present study found that costs of the hospital days and treatment increase by more than NOK 243,000 when deep wound infection exists. This increase along with severity is in line with the findings from some previous studies (C. Edwards et al., 2008; Urban, 2006). Broex and colleagueas (Broex et al., 2009) reviewed a number of studies on SSIs to compare the magnitudes of costs due to SSI in 2009 and found that the cost of SSI was mainly due to prolonged length of stay (LOS). Peel and coworkers (Peel et al., 2013) reported a similar conclusion that duration of hospitalization was one of the most import contributors to SSI cost. This study identifies readmission (56%) as the most important cost driver, followed by reoperation (28%) and prolonged initial hospital stay (11%), therefore, confirming the previous findings.

Results from this study indicates that two-stage revision is the most costly management strategy (NOK 603,486), followed by one-stage revision (NOK 351,856) and resection (NOK 295,880). Though cost estimates were lower, Australian researchers Merollini et al. (2013) reported a

similar cost pattern in their 2013 study. On the other hand, although in the same Australian settings, Peel T.N and colleagues (Peel et al., 2013) reported a total hospital cost for patients treated with one-stage revision of AUD 77,180 (NOK 473,573) and that for patients had arthroplasty resection of AUD 64,007 (NOK 392,722) and further identified one-stage exchange and resection arthroplasty as the indicators of increased cost. This, however, is not a finding that the present study results can support.

An average cost of NOK 198,121 and an increasing risk of revision due to surgical site infection (Dale et al., 2009) in Norway imply that substantial cost savings can be achieved by reducing the number of SSIs. To reduce the number of SSIs, more risk factors are expected to be detected and preventive interventions are to be designed and implemented accordingly. Moreover, as a main cost driver, management strategies for SSI should be optimized to increase the success rate and minimize total cost.

5.2 Limitations and strengths

Compared to previous risk factor analysis based on smaller datasets (Dale, Skramm et al. 2011), the overall sample size from NOIS dataset was sufficient enough to allow for obtaining more statistically significant results. Additionally, the mandatory nature of NOIS, almost complete hospital participation and high completeness of 30-day follow-up have restrained selection bias to a minimal degree.

However, like any research, there are limitations to this study and the results should be interpreted with caution.

A general limitation of this study is associated with the observational nature of a retrospective study. Using observational data that is registered retrospectively means that only association, no causation, can be inferred. For instance, in this study, one can only conclude that infected patients stayed one day longer in hospital than non-infected patients did and assume there is correlation between infection and hospital stay. No statement like surgical site infection makes patient spend one more day in hospital can be made based on this dataset.

The second limitation of this study is about the confounding effect. The number of risk factors included in this study was limited to those reported within the NOIS network. And variables included in the NOIS dataset were not complete, in a sense that data concerning potential confounders such as diabetes, preoperative diagnosis, etc. (Triantafyllopoulos et al., 2015) was

missing. Therefore, the confounding effect could not be completely disregarded although some well-known confounders had been adjusted for.

The third limitation is related to not including 1-year patient follow-up in the analysis. 30-day follow-up is long enough for most procedures, but for those involve implanting, such as hip arthroplasty, 1-year may be a better choice for capturing more information about late surgical site infections.

Costs in this study were estimated in great detail and the estimations covered a comprehensive list of relevant items. Besides, instead of taking from other countries all the unit costs were derived from local official dataset. Aside from these strengths, there are three main limitations in the cost analysis.

Firstly, cost for SSI estimated in this study may have been overestimated by double counting the cost of readmission stay. By its definition, DRG reimbursement cost for revision surgery due to infection should have included the cost of inpatient stay during the "revision period". Given this is the case, the cost of inpatient stay is supposed to be subtracted from the total reimbursement cost. However, lacking information about the proportion that inpatient stay cost constitutes in the reimbursement cost restricts the author from doing so. Another reason for potential cost overestimation lies in the health financing system. DRG reimbursement was assumed as the only way of financing hospitals in this study. In practice, however, only 50% of the hospital cost was funded through DRG system. According to a study comparing actual hospital cost with full DRG reimbursement for liver transplantation in Norway, full DRG reimbursement cost was higher than the actual cost. And this scenario is likely to happen in the study case as well.

The end point of cost analysis was the complete of first revision procedure instead of patients recovering from surgical site infection. While in practice patients are likely to need more than one revision procedures to fully recover from SSI (Merollini et al., 2013). In this sense, the cost might be underestimated.

With these two contradictory effects, it is extremely difficult to conclude whether the costs in this study has been overestimated, underestimated or not.

The last limitation is related to the expert survey. Information obtained from survey cannot completely disregard recall bias and the representativeness of the only survey data remains to be examined. Due to low orthopedic response rate, the quantification of health care resources

was based on the only expert's opinion. Such extremely small sample size could possibly introduce huge variation and uncertainty although the crucial data, such as subsequent hospital stay, was relatively comparable with other studies (Broex et al., 2009). The preplanned bootstrap of cost samples and the test for differences in costs across diagnoses could not be done without more survey data; therefore no variations in costs can be captured. These flaws brought by expert survey and small sample size indicate that using objective information and sufficient sample size are extremely important for an accurate estimation of SSI cost.

6 Conclusion

Of all the risk factors detected in this study, cemented prosthesis and perioperative antibiotic prophylaxis are the modifiable ones and therefore recommended to orthopedic surgeon and infection control personnel for controlling and reducing SSIs following THA. Given these two are common practice in Norway, further studies could focus on including more explanatory variables in risk analysis or on analyzing the effect of various parameters of perioperative antibiotic prophylaxis and cement fixation (such as the time, route and dosage of administration) to establish more effective preventive interventions.

Surgical site infection following primary hip arthroplasty causes significant economic burden for Norwegian hospitals, mainly due to substantial increase in hospital stay and the resource demanding nature of its revision procedures. The high cost of SSI implies that substantial cost savings can be achieved by reducing the number of SSIs, and in turn, highlights the importance of detecting modifiable risk factors for SSI.

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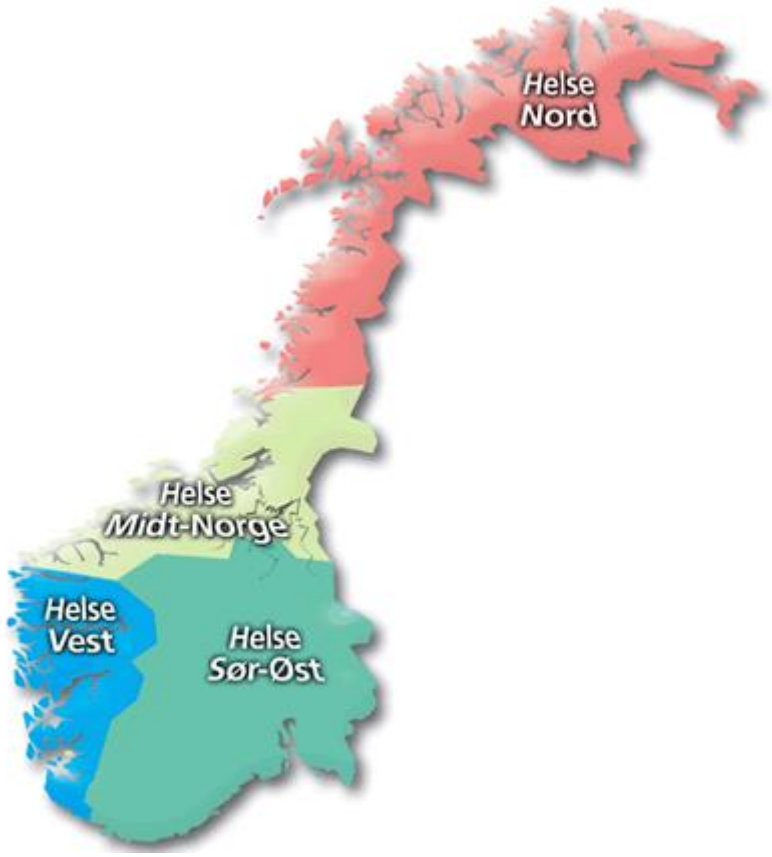
Appendix 1 Regional health authority and its corresponding counties in Norway

Health Region	Corresponding counties
South-Eastern Regional Health Authority	Østfold, Akershus, Oslo, Hedmark, Oppland, Buskerud, Vestfold, Telemark, Aust-Agder, Vest-Agder
Western Norway Regional Health Authority	Rogaland, Hordaland, Sogn og Fjordane
Central Norway Regional Health Authority	Møre og Romsdal, Sør-Trøndelag, Nord-Trøndelag
Northern Norway Regional Health Authority	Nordland, Troms, Finnmark



(Source: liv-lage.no)

Appendix 2 Expert survey of resource used after primary hip arthroplasty for non-infected patients

Infeksjon etter primær total hofteprotese	**Ikke infisert**					
Paientkarakteristika og utfall	Som regel meget godt funksjonelt utfall, 15% medisinsk invaliditet (NAV tabell)					
Innleggelsen der totalprotese ble innsatt (Initial hospitalization)						
Antall dager forlengelse av opphold (Number of days extension of stay)	Dager:	3-7				
Sårbehandling (Wound care)	Type:	Plaster	Antall:	3		
Rtg undersøkelser (X-ray investigation)			Antall:	2		
Antibiotika	Type:	Cefalotin	Dose per dag:	2g X 4	Antall dagers behandling:	1
Blodkulturprøver	Antall:	0				
Bakteriologisk test fra sår	Antall:	0				
Behandling/kontroll hos fastlege/almenlege						
Antall legebesøk	Antall:	1				
Sårbehandling	Type:	Fjerne sting	Antall:	1		
Blodprøver	Antall:	0				
Behandling/kontroll på sykehuspoliklinikk						
Antall poliklinikkbesøk	Antall:	4				
Sårbehandling	Type:	Ingen	Antall:	0		
Rtg undersøkelser			Antall:	4		
Ultralydundersøkelser	Type US	0	Antall:			
Antibiotika (i tillegg til det som ble forskrevet i sykehus eller fastlege)	Type:	Ingen	Dose per dag:	0	Antall dagers behandling:	0
Bakteriologisk test fra sår	Antall:	0				
Reinnleggelser i sykehus						
Antall	Antall:	0				
Gjennomsnittlig varighet (average duration)	Antall dager:	0				
Antall poliklinikkbesøk	Antall:	0				
Sårbehandling	Type:	Ingen	Antall:			
Antibiotika (i tillegg til det som ble forskrevet i sykehus eller fastlege)	Type:	Ingen	Dose per dag:		Antall dagers behandling:	
Reoperasjon	Antall:	Ingen				
Utstyr/Protese brukt	Type:	Vanlig protes	Antall:	1		
Bakteriologisk test fra sår	Antall:	0				
Blodprøver:	Antall:	0				

Appendix 3 Expert survey of resource used after primary hip arthroplasty for patients treated with DAIR or 1-stage revision

Infeksjon etter primær total hofteprotese	**Debridement og retensjon eller 1-trinns revisjon**					
Paientkarakteristika og utfall	Som regel godt funksjonelt utfall, 25% medisinsk invaliditet (NAV tabell)					
Innleggelsen der totalprotese ble innsatt (Initial hospitalization)						
Antall dager forlengelse av opphold (Number of days extension of stay)	Dager:	3-7				
Sårbehandling (Wound care)	Type:	Plaster	Antall:	3		
Rtg undersøkelser (X-ray investigation)			Antall:	2		
Antibiotika	Type:	Cefalotin	Dose per dag:	2g X 4	Antall dagers behandling:	1
Blodkulturprøver	Antall:	0				
Bakteriologisk test fra sår	Antall:	0				
Behandling/kontroll hos fastlege/almenlege						
Antall legebesøk	Antall:	8				
Sårbehandling	Type:	Fjerne sting	Antall:	1		
Blodprøver	Antall:	8				
Behandling/kontroll på sykehuspoliklinikk						
Antall poliklinikkbesøk	Antall:	6				
Sårbehandling	Type:	Ingen	Antall:	0		
Rtg undersøkelser			Antall:	4		
Ultralydundersøkelser	Type US	Leddpunksjo	Antall:	1		
Antibiotika (i tillegg til det som ble forskrevet i sykehus eller fastlege)	Type:	Se reinnl.				
Bakteriologisk test fra sår	Antall:	1				
Reinnleggelser i sykehus						
Antall	Antall:	1				
Gjennomsnittlig varighet (average duration)	Antall dager:	14				
Antall poliklinikkbesøk	Antall:	3				
Sårbehandling	Type:	Plaster	Antall:	5		
Antibiotika (i tillegg til det som ble forskrevet i sykehus eller fastlege)	Type:	Rimactan	Dose per dag:	300mg x	Antall dagers behandling:	90
	Type:	Vancomicin	Dose per dag:	1g x 2		7
		Ciproxin		750 mg x 2		83
Reoperasjon	Antall:	1	Samlet varighet:	2 t		
Utstyr/Protese brukt	Type:	Bytte hode o	Antall:	1		
Bakteriologisk test fra sår	Antall:	5-8				
Blodprøver:	Antall:	14				

Appendix 4 Expert survey of resource used after primary hip arthroplasty for patients treated with 2-stage revision

Infeksjon etter primær total hofteprotese	**2-trinns revisjon**					
Paientkarakteristika og utfall	Brukbart funksjonelt resultat, 35% medisinsk invaliditet (NAV tabell)					
Innleggelsen der totalprotese ble innsatt (Initial hospitalization)						
Antall dager forlengelse av opphold (Number of days extension of stay)	Dager:	3-7				
Sårbehandling (Wound care)	Type:	Plaster	Antall:	3		
Rtg undersøkelser (X-ray investigation)			Antall:	2		
Antibiotika	Type:	Cefalotin	Dose per dag:	2g X 4	Antall dagers behandling:	1
Blodkulturprøver	Antall:	0				
Bakteriologisk test fra sår	Antall:	0				
Behandling/kontroll hos fastlege/almenlege						
Antall legebesøk	Antall:	8				
Sårbehandling	Type:	Fjerne sting	Antall:	1		
Blodprøver	Antall:	8				
Behandling/kontroll på sykehuspoliklinikk						
Antall poliklinikkbesøk	Antall:	8				
Sårbehandling	Type:	Ingen	Antall:	0		
Rtg undersøkelser			Antall:	4		
Ultralydundersøkelser	Type US	Leddpunksjo	Antall:	1		
Antibiotika (i tillegg til det som ble forskrevet i sykehus eller fastlege)	Type:	Se reinnl				
Bakteriologisk test fra sår	Antall:	1				
Reinnleggelser i sykehus						
Antall	Antall:	2				
Gjennomsnittlig varighet (average duration)	Antall dager:	21				
Antall poliklinikkbesøk	Antall:	6				
Sårbehandling	Type:	Plaster	Antall:	10		
Antibiotika (i tillegg til det som ble forskrevet i sykehus eller fastlege)	Type:	Vancomicin	Dose per dag:	1g x 2	Antall dagers behandling:	7
		Ekvacillin		2g x 4		7
		Diclocil		1g x 4		76
Reoperasjon	Antall:	2	Samlet varighet:	5 t		
Utstyr/Protese brukt	Type:	Antibiotikasp	Antall:	1		
		Revisjons protese		1		
Bakteriologisk test fra sår	Antall:	10-16				
Blodprøver:	Antall:	20				

Appendix 5 Expert survey of resource used after primary hip arthroplasty for patients treated with prosthesis resection

Infeksjon etter primær total hofteprotese	**Reseksjon**					
Paientkarakteristika og utfall	Gamle og syke pasienter, dårlig funksjonelt resultat, 45% medisinsk invaliditet (NAV tabell)					
Innleggelsen der totalprotese ble innsatt (Initial hospitalization)						
Antall dager forlengelse av opphold (Number of days extension of stay)	Dager:	3-7				
Sårbehandling (Wound care)	Type:	Plaster	Antall:	3		
Rtg undersøkelser (X-ray investigation)			Antall:	2		
Antibiotika	Type:	Cefalotin	Dose per dag:	2g X 4	Antall dagers behandling:	1
Blodkulturprøver	Antall:	0				
Bakteriologisk test fra sår	Antall:	0				
Behandling/kontroll hos fastlege/almenlege						
Antall legebesøk	Antall:	8				
Sårbehandling	Type:	Fjerne sting	Antall:	1		
Blodprøver		8				
Behandling/kontroll på sykehuspoliklinikk						
Antall poliklinikkbesøk	Antall:	4				
Sårbehandling	Type:	Ingen	Antall:	0		
Rtg undersøkelser			Antall:	2		
Ultralydundersøkelser	Type US	Ledpunksjon	Antall:	1		
Antibiotika (i tillegg til det som ble forskrevet i sykehus eller fastlege)	Type:	Se reinnl				
Bakteriologisk test fra sår	Antall:	1				
Reinnleggelser i sykehus						
Antall	Antall:	1				
Gjennomsnittlig varighet (average duration)	Antall dager:	14				
Antall poliklinikkbesøk	Antall:	3				
Sårbehandling	Type:	Plaster	Antall:	10		
Antibiotika (i tillegg til det som ble forskrevet i sykehus eller fastlege)	Type:	Vancomicin	Dose per dag:	1g x 2	Antall dagers behandling:	7
		Ekvacillin		2g x 4		7
		Diclocil		1g x 4		28
Reoperasjon	Antall:	1	Samlet varighet:	3 t		
Utstyr/Protese brukt	Type:	Fjerne protese				
Bakteriologisk test fra sår	Antall:	5-8				
Blodprøver:	Antall:	14				

Appendix 6 Wound contamination classification

Wound contamination	
Class	**Definition**
I	Clean surgical wounds show no signs of inflammation and do not involve the respiratory, gastrointestinal or genitourinary tracts. Laparoscopic surgeries, surgeries involving the skin (such as biopsies), eye or vascular surgeries are good examples.
II	Clean-contaminated wounds are clean wounds with a higher risk of infection such as those involving the gastrointestinal, respiratory or genitourinary tracts, as long as the surgery is uncomplicated. Any wound opened to remove pins or wires, chest procedures, ear surgeries or gynecologic procedures are considered class II surgical wounds.
III	Contaminated wounds are created when an outside object comes in contact with the wound. This could be a bullet, knife blade or other pointy object. Or the contamination could be caused by large amounts of spillage from the GI tract into the wound. Any highly inflamed or infected tissue around a surgical wound is considered contaminated.
IV	Dirty-infected surgical wounds include those with a foreign object lodged in the wound (such as a bullet or other debris). This class also includes traumatic wounds from a dirty source where the treatment was delayed, infected surgical wounds or any wound that has been exposed to pus or fecal matter.